Prolonged Tracheal Intubation and the Association Between Patent Ductus Arteriosus and Bronchopulmonary Dysplasia: A Secondary Analysis of the PDA-TOLERATE trial

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In the PDA-TOLERATE trial, persistent (even for several weeks) moderate to large patent ductus arteriosus (PDA) was not associated with an increased risk of BPD when the infant required <10 days of intubation. However, in infants requiring intubation for ≥10 days, prolonged PDA exposure (≥11 days) was associated with an increased risk of moderate/severe BPD. *(J Pediatr 2021;229:283-88).*

Between 50% and 70% of infants born at <28 weeks of gestation have a patent ductus arteriosus (PDA) that persists for weeks after birth.[1] Early PDA closure can decrease the incidence of several neonatal morbidities that occur during the first week after birth, such as dopamine-dependent hypotension and early hemorrhagic pulmonary edema, as well as the intensity of respiratory support.[2-6] Whether exposure to a PDA shunt increases the risks of later neonatal morbidities, such as bronchopulmonary dysplasia (BPD), is still unclear. None of the randomized clinical trials (RCTs) performed to date has found a relationship between therapies intended to close the PDA and the risk of developing BPD.[5,7-12] Unfortunately, however, when these trials were designed, there was little information available to determine which infants with a PDA were actually at risk for BPD and might benefit from enrollment in such a trial. Little attention was paid to the magnitude of the PDA shunt, the duration of shunt exposure, or the infant's need for respiratory support.

Several recent single-center observational studies have shown that infants with small PDA shunts do not appear to be at increased risk for developing BPD. Instead, an association between PDA and BPD is apparent only when moderate to large shunts persist beyond 7-14 days.[13-17] An infant's need for invasive respiratory support also may play an important role in determining whether prolonged PDA exposure is associated with BPD. A recent single-center study found an association between BPD and exposure to a moderate to large PDA only when infants required mechanical ventilation and intubation for ≥10 days.[17] The incidence of BPD among infants who required intubation for shorter durations (<10 days) was the same irrespective of whether the ductus closed soon after birth or whether it persisted as a moderate to large shunt for several weeks.[17] The results of these single-center studies need to be confirmed by other centers before they can be considered useful, consistent criteria for identifying infants at risk for developing BPD if the ductus fails to close after birth.

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The PDA-TOLERATE trial (ClinicalTrials.gov: NCT01958320) was a prospective randomized controlled trial conducted between January 2014 and June 2017 at 17 international neonatal intensive care centers.[11] The trial

BPD	Bronchopulmonary dysplasia
CPD	Continuous positive airway pressure
NEC	Necrotizing enterocolitis
PDA	Patent ductus arteriosus
RCT	Randomized clinical trial
SIP	Spontaneous intestinal perforation

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enrolled infants at <$28^{0/7}$ weeks of gestation to determine whether routine pharmacologic treatment of PDA at the end of the first postnatal week would reduce neonatal morbidity compared with a conservative approach that delayed PDA drug treatment for at least another 7-10 days. The trial demonstrated that routine PDA treatment at the end of the first week did not reduce PDA ligations or any of the prespecified secondary outcomes like BPD.

We performed a secondary analysis of the data from the PDA-TOLERATE trial to determine whether an infant's need for invasive respiratory support plays a role in shaping the relationship between PDA exposure and BPD. We were particularly interested in determining whether the association between PDA exposure and BPD depended on the infant's duration of tracheal intubation.

Methods

We used deidentified data from the multicenter PDA-TOLERATE trial (NCT01958320). Institutional Review Board approval and written informed parental consent were obtained before patient enrollment into the trial. The trial enrolled 202 infants at <$28^{0/7}$ weeks of gestation at the end of the first week (between 6 and 14 days) who still had a persistent moderate to large PDA and required continuing respiratory support with either nasal continuous positive airway pressure (CPAP) or intubation and mechanical ventilation. Infants were randomized to receive either "early routine" pharmacologic PDA treatment (n = 104) or a "conservative approach" (n = 98) that delayed pharmacologic treatment until at least 7 days after randomization. Infants randomized to the conservative approach were not eligible for pharmacologic PDA treatment unless 1 or more prespecified respiratory and/or cardiovascular "rescue" criteria were met.[11] Rescue surgical ligation was used in both trial groups only if pharmacologic agents failed to constrict the PDA or were contraindicated.[18,19] The decision to use rescue ligation was left to the attending neonatologist. Full details of the PDA-TOLERATE trial, including screening, echocardiographic analyses, inclusion and exclusion criteria, enrollment, drug treatment protocols, rescue criteria, and definitions of study variables and outcomes, have been published elsewhere.[11]

Echocardiographic studies in the PDA-TOLERATE trial were performed according to the study protocol and schedule for examinations[11] and included 2-dimensional imaging, M-mode, color flow mapping, and Doppler interrogation as described previously.[19,20] A moderate to large PDA was defined by a ductus internal diameter ≥1.5 mm (or a PDA:left pulmonary artery diameter ≥0.5) and one or more of the following echocardiographic criteria: left atrium:aortic root ≥1.6, ductus flow velocity ≤2.5 m/second, left pulmonary artery diastolic flow velocity >0.2 m/second, and/or reversed diastolic flow in the descending aorta. PDAs that did not meet these criteria were considered "constricted" (small or closed) and not eligible for enrollment or treatment. The cardiologists or echocardiography-trained neonatologists reading the echocardiograms were unaware of the infants' treatment assignments.

All infants had an echocardiogram performed at the time of randomization. A repeat echocardiogram was performed in both the conservative treatment and early treatment groups between 5 and 7 days after randomization. Infants with a constricted ductus were examined daily for a change in clinical symptoms indicative of a reopened, moderate to large PDA (systolic murmur or hyperdynamic precordium). If either of these occurred, an echocardiogram was performed within 24 hours. In addition, routine echocardiograms were performed every 2-3 weeks in infants with a "constricted" PDA until ductus closure or hospital discharge. Infants with a persistent moderate to large PDA were followed with frequent (every 7-14 days) echocardiograms to determine when ductus constriction occurred. Echocardiograms were performed until ductus closure or hospital discharge.

The duration of exposure to a moderate to large PDA was calculated and expressed in days. The day of birth was considered day 0. All infants in the trial had a persistent moderate to large PDA at the time of enrollment and were assumed to have been exposed to a moderate to large PDA since birth. The time of ductus constriction was assumed to have occurred at the halfway point between the last examination with a moderate to large PDA and the first examination with a constricted ductus. When reopening of the PDA occurred after documented ductus constriction, the additional exposure to the reopened moderate to large PDA shunt was calculated as the number of days from the echocardiogram demonstrating the reopened moderate to large shunt to the time of ductus constriction (ie, the halfway point between the last examination with a moderate to large PDA and the first examination with a constricted ductus). The duration of exposure to the reopened PDA was added to the initial moderate to large PDA shunt exposure.

Our primary outcome for this secondary analysis was the incidence of BPD, both any grade and the incidence of moderate to severe BPD (grades 2 and 3), as defined by Jensen et al.[21] This definition categorizes BPD severity according to the mode of respiratory support administered at 36 weeks of postmenstrual age, regardless of the previous duration or current level of oxygen therapy. Infants with grade 2 or 3 BPD are reported to have a 47% chance of having late death or serious childhood respiratory morbidity, compared with a 10% risk in infants with no BPD or a 19% risk in those with grade 1 BPD.[21] All study infants (except those requiring CPAP with ≥30% oxygen or mechanical ventilation) first underwent a modified room air challenge test between $36^{0/7}$ and $36^{6/7}$ weeks.[22] Those who failed the test (or who required CPAP with ≥30% oxygen or mechanical ventilation) were classified as "BPD any grade" and were further classified based on the severity graded diagnostic criteria of Jensen et al.[21] Infants were classified as grade 2-3 BPD if they required a nasal cannula flow rate >2 L/min, noninvasive positive airway pressure, or invasive mechanical ventilation between $36^{0/7}$ and $36^{6/7}$ weeks. None of the infants who

passed the room air challenge test ever met the criteria for BPD (grade 2 or 3).

Statistical Analyses

The χ^2, Fisher exact, Mann-Whitney, and Student *t* tests were used to compare groups for categorical and parametric variables. Our primary goal was to examine the effect of invasive mechanical ventilation on the relationship between the variable duration of PDA exposure and the outcome BPD (both any grade and grade 2-3). Previous single-center observational studies reported that infants <28 weeks of gestation who were exposed to a moderate to large PDA for longer than 7-14 days had a significantly higher incidence of BPD than those exposed to shorter durations of ductus patency; in addition, once the threshold exposure of 7-14 days was reached, additional exposure (>15 days) was not associated with additional increases in the incidence of BPD.[15,17] Therefore, in this study, the variable duration of PDA exposure was defined as a binary categorical variable: exposure to a moderate to large PDA for <11 days and ≥11 days. Similarly, the variable duration of invasive mechanical ventilation was defined as a binary variable (tracheal intubation <10 days and ≥10 days), because previous studies have shown that the variable tracheal intubation ≥10 days was both significantly associated with the outcome BPD[17] and more strongly associated with the outcome of BPD than other neonatal variables.[23] The variable duration of tracheal intubation included both consecutive and nonconsecutive days of intubation.

Results

Among the 202 infants in the PDA-TOLERATE trial, 25 infants were exposed to a moderate to large PDA for <11 days and 177 were exposed for ≥11 days. Twenty-six infants died before being evaluated for BPD at 36 weeks (**Figure 1**; available at www.jpeds.com). There was no difference in the death rate before 36 weeks between infants exposed to a moderate to large PDA for <11 days and those exposed for ≥11 days (**Figure 1**).

Our study population comprised the 176 infants evaluated for BPD at 36 weeks (**Table**). Among the perinatal or neonatal demographic characteristics listed in the **Table**, only 2 characteristics were significantly different between the 2 PDA exposure groups: infants exposed to a moderate to large PDA for ≥11 days were more likely to be randomized to the conservative approach and were more likely to be randomized at a later postnatal age (**Table**).

Overall, 51% (90 of 176) of the study population had BPD of any grade; 26% (46 of 176) had moderate to severe BPD (ie, grade 2-3). As reported previously,[23] the incidence of BPD was significantly greater among infants who received tracheal intubation for ≥10 days compared with those intubated at <10 days (BPD any grade: intubated <10 days, 27% [24 of 88]; intubated ≥10 days, 75% [66 of 88]; $P < .0001$; BPD grade 2-3: intubated <10 days, 11% [10 of 88]; intubated ≥10 days, 41% [36 of 88]; $P < .0001$).

Table. Demographic characteristics of infants who were evaluated for bronchopulmonary dysplasia at 36 weeks corrected age after being exposed to a moderate to large PDA shunt for <11 days or for ≥11 days

Variables	Duration of exposure to a moderate to large PDA		
	<11 days	≥11 days	*P* value
Number of patients	20	156	
Prenatal variables			
Multiple gestation, %	30	32	
Preeclampsia, %	20	18	
Maternal diabetes, %	10	4	
Chorioamnionitis, %	15	15	
Antenatal betamethasone <24 hours, %	45	33	
Cesarean delivery, %	70	71	
Neonatal variables			
Gestation, wk, mean ± SD*	25.7 ± 1.2	25.9 ± 1.1	
Gestational age ≤25 wk, %	60	49	
Birth weight, g, mean ± SD	818 ± 125	810 ± 175	
Small for gestational age, %†	0	8	
Caucasian, %	45	51	
Male sex, %	50	45	
5-minute Apgar score ≤5, %	40	32	
Intubated in the delivery room, %	65	67	
Intubated during first 24 hours, %	95	90	
Still intubated at 24 hours, %	50	65	
Dopamine in first 72 hours after birth, %	35	33	
ICH (grade 3-4), %‡	10	11	
PDA-TOLERATE age at randomization, d, mean ± SD	6.3 ± 1.1	8.5 ± 2.1	<.001
PDA-TOLERATE conservative group, %	10	56	<.001
Intubated at enrollment, %	60	45	
Postnatal steroids, %	30	44	
Early-onset bacteremia, %§	10	2	
Late-onset bacteremia, %¶	20	22	
SIP/NEC, %**	10	14	
Any pharmacologic PDA treatment, %††	90	71	
PDA ligation, %	0	13	
Duration of moderate/large PDA exposure, d, median (IQR)	10 (9-10)	26 (19-49)	<.001
Duration of intubation, d, median (IQR)	8.5 (0-16.5)	9.0 (0-27)	
Duration of intubation ≥10 d, %	50	50	

Demographic characteristics of infants who were evaluated for BPD at 36 weeks corrected age after being exposed to a moderate to large PDA shunt for <11 days or for ≥11 days.
Only *P* values ≤.150 are reported.
*Gestational age was determined by the date of last menstrual period and ultrasounds performed before 24 weeks gestation.
†Small for gestational age: infants with birthweight-for-gestational age *z*-scores <-1.29 using the growth curves from Fenton and Kim.[24]
‡ICH (grade 3 or 4): serious intraventricular hemorrhage, defined as grade 3 or 4 intraventricular hemorrhage using the four-level grading system.[25]
§Early-onset bacteremia: culture-positive bacteremia occurring ≤3 days after birth.
¶Late-onset bacteremia: culture-positive bacteremia occurring ≥4 days after birth.
**SIP/NEC: spontaneous intestinal perforation occurring before 10 days, or necrotizing enterocolitis, defined as Bell classification II or greater (either medically or surgically treated).[26]
††Any PDA treatment: infants who received PDA treatment as part of the early PDA treatment protocol or later rescue PDA treatment.

Our main objective was to determine whether the amount of invasive respiratory support that infants received also affected the relationship between PDA exposure and BPD. Among infants who received <10 days of intubation, prolonged exposure to a moderate to large PDA (even for several weeks) did not appear to be associated with an increased risk of BPD (**Figure 2**): BPD any grade: PDA <11 days, 30% (3 of 10); PDA ≥11 days, 27% (21 of 78); $P = 1.00$; BPD grade 2-3: PDA <11 days, 10% (1 of 10), PDA ≥11 days, 12% (9 of 78); $P = 1.00$.

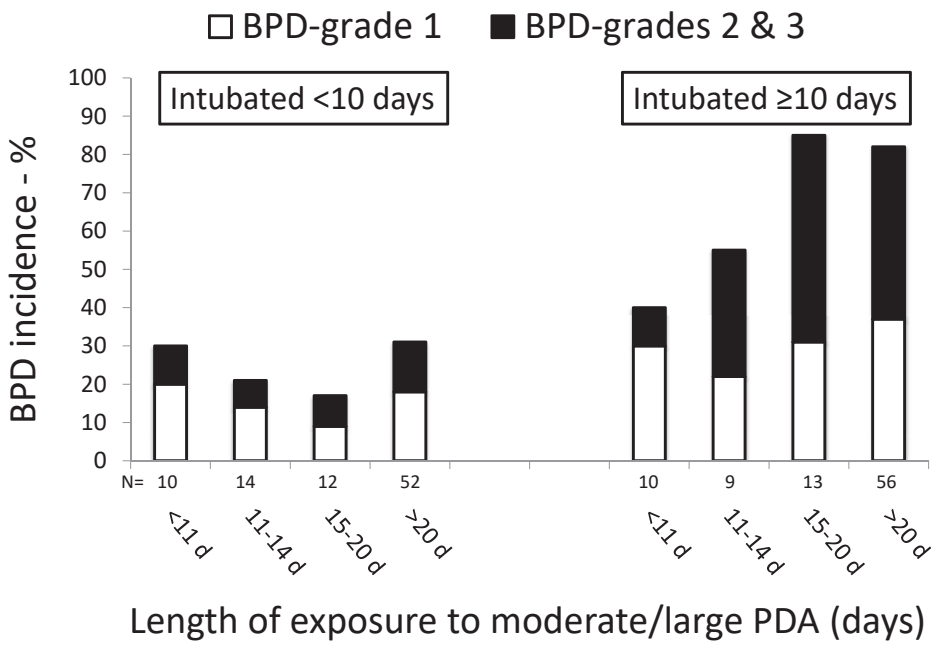

Figure 2. Relationship between PDA exposure and the outcomes BPD of any grade and BPD grades 2 and 3 among infants intubated for <10 days or ≥10 days. The height of the bars represents the incidence of BPD of any grade. The clear portion of the bar represents the incidence of BPD grade 1. The solid portion of the bar represents the incidence of BPD grade 2-3. Infants exposed to a moderate to large PDA for ≥11 days were arbitrarily divided into 3 exposure subgroups (11-14 days, 15-20 days, and >20 days) to illustrate how incremental increases in exposure (beyond 10 days) affects the association between BPD and the presence of a persistent PDA.

On the other hand, when this relationship was examined among infants who required tracheal intubation for ≥10 days, prolonged exposure to a moderate to large PDA was associated with a significant increase in the risk of developing BPD (Figure 2): BPD any grade: PDA <11 days, 40% (4 of 10); PDA ≥11 days, 79% (62 of 78); $P = .01$; BPD grade 2-3: PDA <11 days, 10% (1 of 10); PDA ≥11 days, 45% (35 of 78); $P = .04$.

Discussion

Our secondary analysis of the multicenter PDA-TOLERATE trial agrees with the findings from previous single-center observational studies that have reported an association between the duration of PDA exposure and the incidence of BPD,[13-17] and extends those studies' findings to more narrowly identify which infants with a moderate to large PDA are at greatest risk for developing BPD. In our study, prolonged PDA exposure (≥11 days) was associated with an increased incidence of both BPD any grade and moderate-severe forms of BPD (grade 2-3). However, the increased risk of BPD associated with prolonged PDA exposure was seen only in infants who also received prolonged intubation and mechanical ventilation (≥10 days). The incidence of BPD among infants who received less ventilatory support (intubation for <10 days) was the same whether the ductus closed shortly after birth or whether it persisted as a moderate to large shunt for several weeks. Although our results do not prove a cause-and-effect relationship, they do indicate that the persistence of a moderate to large PDA shunt beyond 10 days in infants requiring prolonged intubation may be a useful biomarker for identifying infants at increased risk for BPD. In addition, our results suggest that if a clinician's sole purpose for wanting to close a PDA is to decrease the incidence of BPD, then infants who require a shorter duration of intubation (<10 days) may not need to have their ductus closed even if they do have a moderate to large PDA shunt that persists for several weeks.

Our study has several limitations. As an observational study, it cannot distinguish between causation and association. Because echocardiograms were performed every 7 days during the first 3 weeks, the exact duration of exposure to the moderate to large PDA was an assumption based on the halfway point between the last examination with a moderate to large PDA and the first examination with a constricted ductus. In addition, we focused our study on infants with a persistent PDA beyond the first week, and thus cannot address whether brief exposures to a moderate to large PDA during the first week could have altered the study outcomes. However, the effects of PDA exposure during the first week have been addressed by several previous RCTs, which found no noticeable effect on the incidence of BPD.[5,7-10] The relatively small size of our study may have made it difficult to detect significant differences among

some of our PDA exposure subgroups. Even though there were no significant differences in any of the neonatal demographic characteristics between infants exposed to a moderate to large PDA for <11 days and those exposed for ≥11 days, unmeasured differences in practice might have affected the rate of BPD.

Our results may help to interpret the findings of 2 recently reported PDA treatment RCTs (PDA-TOLERATE trial and Nonintervention vs Oral Ibuprofen trial).[11,12] In contrast to earlier PDA treatment RCTs, in which PDA shunt magnitude was usually unknown, both trials were designed to exclusively enroll infants with moderate to large PDAs. Although the infants enrolled in these trials were the infants most likely to be affected by the presence of a persistent PDA, neither trial found that the drugs used to close the PDA had any effect on the risk of BPD. We speculate that a possible explanation for the failure of both trials to detect a causal relationship between PDA exposure and BPD is that infants in the early treatment arms of both trials may have been exposed to moderate to large PDA shunts for too long an interval for the infants to receive any benefit from treatment. Both studies suffered from a low rate of PDA closure in the early treatment arm of the trial. In the PDA-TOLERATE trial, among the infants most likely to develop BPD (those ventilated for ≥10 days), only 22% of the early treatment enrollees constricted their ductus before 11 days and 78% of the early treatment group were ultimately exposed to a prolonged moderate to large PDA shunt that persisted for ≥11 days.[11] Similarly, only 20% of the infants in the early treatment arm of the Nonintervention vs Oral Ibuprofen trial constricted their ductus before 2 weeks.[12] Successful closure was even less prevalent among infants born between 23 and 26 weeks of gestation in the Nonintervention vs Oral Ibuprofen trial, where only 8% constricted their ductus before 2 weeks. In both studies, the failure of early routine PDA treatment to decrease the incidence of BPD might be attributable to the low therapeutic efficacy of the drugs used for PDA closure. Future RCTs will need to find reliable treatments that can close the PDA before 11 days if we are ever to learn whether early PDA closure will or will not decrease the incidence of BPD.

In conclusion, in the PDA-TOLERATE trial, which tolerated moderate to large PDAs for the first week in infants $<28^{0/7}$ weeks of gestation, the presence of a PDA shunt was associated with an increased risk of BPD when it persisted beyond 10 days and the infant also required prolonged intubation (≥10 days). On the other hand, prolonged exposure to a PDA (even for several weeks) did not appear to be associated with an increased risk of BPD if the infant required <10 days of intubation. ■

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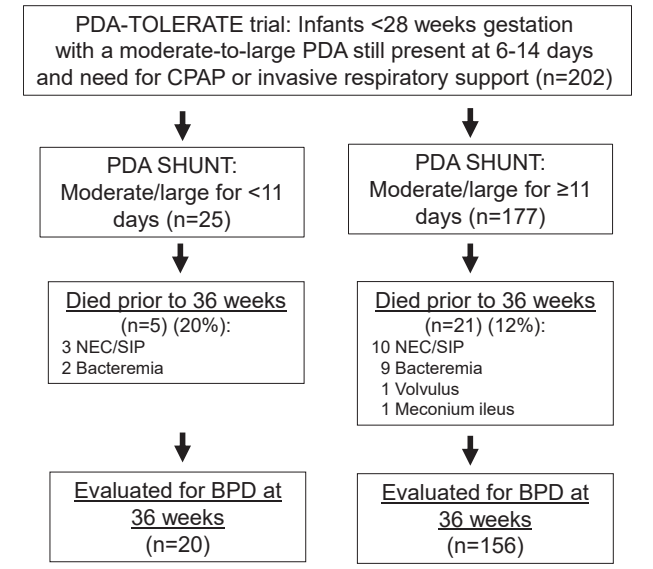

Figure 1. Flow diagram of patient distribution in the PDA-TOLERATE trial: number of infants exposed to a moderate to large PDA shunt for <11 days or ≥11 days who were evaluated for BPD at 36 weeks postmenstrual age.