Lack of Equipoise in the PDA-TOLERATE Trial: A Comparison of Eligible Infants Enrolled in the Trial and Those Treated Outside the Trial

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The PDA: TO LEave it alone or Respond And Treat Early trial compared the effects of 2 strategies for treatment of patent ductus arteriosus (PDA) in infants <$28^{0/7}$ weeks of gestation; however 137 potentially eligible infants were not recruited and received treatment of their PDA outside the PDA-TOLERATE trial due to "lack-of-physician-equipoise" (LPE). Despite being less mature and needing more respiratory support, infants with LPE had lower rates of mortality than enrolled infants. Infants with LPE treated before day 6 had lower rates of late respiratory morbidity than infants with LPE treated ≥day 6. *(J Pediatr 2019; ■:1-7).*

Trial registration ClinicalTrials.gov: NCT01958320.

PDA-TOLERATE (the PDA: TO LEave it alone or Respond And Treat Early Trial; NCT01958320) was a multicenter, randomized, controlled trial that compared the effects of 2 strategies for the treatment of patent ductus arteriosus (PDA) in infants <$28^{0/7}$ weeks of gestation.[1] The trial enrolled 202 infants with moderate-to-large PDA who required respiratory support. Infants were randomized at the end of the first week to receive either routine pharmacologic treatment or a conservative approach that delayed pharmacologic treatment until prespecified respiratory and/or cardiovascular "rescue" criteria were met. The trial demonstrated that routine PDA treatment at the end of the first week did not reduce PDA ligations or presence of a PDA at discharge, nor did it reduce any of the prespecified secondary outcomes (death, bronchopulmonary dysplasia [BPD], or BPD or death before 36 weeks).

Physicians caring for infants in the PDA-TOLERATE trial stated before joining the trial that they had equipoise regarding the risks and benefits of each of the trial's therapeutic arms and were willing to recruit and enroll all eligible infants. However, 18% of potentially eligible infants were not recruited into the trial due to the medical team's desire to use pharmacologic PDA treatment outside the confines of the trial (lack of physician equipoise [LPE]). In these cases, the physicians elected to exclude the infants from the trial and treat them either because of a perceived risk associated with randomization to the conservative approach or because they felt the infants were "too sick to wait" for randomization at the end of the first week.

Because these potentially eligible infants were excluded from the trial, we designed the following study to determine whether the infants enrolled in PDA-TOLERATE really reflected the population of infants the trial was designed to examine (namely, those <$28^{0/7}$ weeks of gestation with moderate-to-large PDA). We wanted to determine whether infants treated outside the trial, due to LPE, differed from those enrolled in the trial, both in their early clinical characteristics and in their ultimate clinical outcomes. We hypothesized that infants who were excluded due to LPE would be less mature and "sicker" than those who were enrolled in PDA-TOLERATE and would be at greater risk for developing neonatal morbidity.

BPD	Bronchopulmonary dysplasia
LPE	Lack of physician equipoise
PDA	Patent ductus arteriosus
PDA-TOLERATE	The PDA: TO LEave it alone or Respond And Treat Early Trial

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Supported by grants from the Gerber Foundation; US Public Health Service; National Heart, Lung, and Blood Institute (HL109199); National Center for Advancing Translational Sciences, National Institutes of Health (through UL1 TR001872, UL1 TR000004, and UL1TR001873); and a gift from the Jamie and Bobby Gates Foundation. The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2019.05.049

Methods

Our observational study used data from 2 study data sets; data from infants enrolled in PDA-TOLERATE (a prospective randomized controlled trial conducted between January 2014 and June 2017 at 17 international sites[1]) and data from infants screened for PDA-TOLERATE who were excluded from the trial (even though they were potentially eligible) because the medical team wanted to use pharmacologic PDA treatment outside the confines of the study. Institutional review board approvals were obtained at the study sites for both the parent PDA-TOLERATE trial and the ancillary study examining patients not enrolled due to LPE.

Full details of PDA-TOLERATE, including screening, echocardiographic analyses, inclusion and exclusion criteria, enrollment and drug treatment protocols, and definitions of study variables and outcomes, have been published elsewhere.[1] Infants $<28^{0/7}$ weeks of gestation were enrolled in PDA-TOLERATE if they were between 6 and 14 days old, had a moderate-to-large PDA, and were receiving greater than minimal respiratory support, defined as either positive pressure ventilation, continuous positive airway pressure, or high-flow nasal cannula support with >2 L/min cannula flow and fraction of inspired oxygen >0.25.[1]

Eligible infants were excluded from participation if they received treatment with indomethacin or ibuprofen before randomization, had chromosomal anomalies, congenital or acquired gastrointestinal anomalies, previous episodes of necrotizing enterocolitis or intestinal perforation, active pulmonary hemorrhage at the time of enrollment, or contraindications to the use of indomethacin or ibuprofen (eg, hydrocortisone or dexamethasone administration within preceding 24 hours, urine output <1 mL/kg/h during the preceding 8 hours, serum creatinine >1.6 mg/dL, platelet count <50 000/mm^3, or abnormal coagulation studies). Sixteen of the 17 centers also excluded infants if they needed inotropic support for hypotension at the time of enrollment.[1] Except for the difference in timing of PDA treatment, the 2 arms of the study used the same treatment protocols at each site for feeding advances, ventilator management, fluid management, or management of hypotension.

Study coordinators, who were not blinded to the patients' treatment assignments, collected information from infants enrolled in PDA-TOLERATE and all eligible infants who were excluded from the trial due to LPE. All variables were defined a priori before data extraction. The reasons given during interviews with the medical teams for not enrolling the infants and excluding them from the trial were either "this infant is too sick and I don't want to wait until 6 days before starting treatment," or "this infant should be treated and I do not want to risk the possibility that he/she could be randomized to the conservative approach." Infants who were treated outside of the trial due to LPE had echocardiographic assessments to confirm the presence of a moderate-to-large PDA and received the same drug treatment protocol used in PDA-TOLERATE at that site.[1]

Two hundred and two infants were enrolled in PDA-TOLERATE; 152 were treated outside of the trial due to LPE. Sixteen of the 17 sites submitted data for patients at their site who were not enrolled due to LPE (n = 137). One site, that enrolled only 2 patients in PDA-TOLERATE, was unable to furnish data for the 15 patients at that site who were not enrolled due to LPE.

Statistical Analyses

Our primary goal was to compare the demographic variables and neonatal outcomes between infants who were treated outside PDA-TOLERATE (due to LPE) and those that were enrolled in the trial. Stata Statistical Software: Release 14 (StataCorp LP, College Station, Texas) was used for all statistical analysis. χ^2 tests were used to compare categorical variables, Student *t* tests were used to compare parametric variables, and Wilcoxon rank sum tests were used to compare nonparametric variables. *P* values <.05 were considered to be significant.

Among infants treated outside the trial due to LPE, we also used logistic regression to examine the relationship between the age at PDA treatment and neonatal morbidity. To perform this analysis, we created statistical models that included our variable of interest (postnatal age at treatment) in addition to the other demographic variables that have been associated with the outcome of interest ("BPD or death"): betamethasone ≥24 hours, small for gestational age, white race, intubation at 24 hours, dopamine during first 72 hours after birth, early-onset bacteremia, and late-onset bacteremia. To determine which of these demographic variables should be included in the final statistical model, we first performed a logistic regression to determine the OR for our variable of interest (postnatal age at treatment) alone (basic model). Next, we added one of the other demographic variables to the basic model and re-ran the logistic regression to determine to what extent the OR for the variable postnatal age at treatment was altered by the addition of the new variable. If the addition of the new variable altered the OR of postnatal age at treatment by >10%, we considered it to be an important demographic variable that should be added to the final adjusted model. We repeated this step with each of the other demographic variables. The final adjusted model contained the variables postnatal age at treatment plus gestational age plus all of the other important demographic variables.

Results

Infants who were treated outside PDA-TOLERATE due to LPE were significantly younger, less likely to have received antenatal betamethasone, more likely to have needed surfactant, and more likely to have needed intubation during the first weeks after delivery than were infants who were enrolled in the trial (**Table I**).[2,3] Despite the difference in these risk factors for neonatal morbidity, infants who were treated outside PDA-TOLERATE had a similar or significantly lower incidence of late neonatal morbidity than infants enrolled in the trial (**Table I**).

Table I. Comparison of prenatal and neonatal characteristics of infants enrolled in the PDA-TOLERATE trial with those who were eligible for the trial but were not enrolled because the infant's medical team wanted to treat the PDA outside of the study

Characteristics	PDA-TOLERATE enrollees (n = 202)	Infants NOT enrolled (infants treated due to physician preference) (n = 137)	*P* value*
Prenatal variables			
Maternal age, y, mean ± SD	29.4 ± 6.4	28.7 ± 6.0	
Multiple gestation, %	32	36	
Premature rupture of membranes, %	20	21	
Preeclampsia, %	18	19	
Chorioamnionitis, %	16	14	
Diabetes, %	4	7	
Cesarean delivery, %	69	76	
Betamethasone ≥24 h, %	64	53	.030
Neonatal variables			
Gestation, wk, mean ± SD	25.8 ± 1.2	25.5 ± 1.2	.017
Gestation ≤25 wk, %	52	61	.108
Birth weight, g, mean ± SD	800 ± 169	785 ± 179	
Small for gestational age, %	7	9	
Male, %	45	47	
White, %	52	35	.002
Apgar (10-min) ≥6, %	93	96	
Surfactant, %	91	97	.028
Dopamine during first 72 h after birth, %	34	21	.010
Intubated in delivery room, %	69	85	.001
Intubated at 24 h, %	64	74	.076
Intubated at 8 d, %	50	64	.011
Intubated at 15 d, %	47	63	.002
Postnatal steroids, %	45	49	
Early-onset bacteremia, %	4	4	
Late bacteremia, %	26	18	.114
NEC or GI perforation, %	19	16	
Age when ductus constricted (small or closed), d, median (IQR)	22 (14-46)	11 (7-21)	<.001
Age at enrollment (PDA-TOLERATE) or Decision to treat PDA, d, mean ± SD	8.2 ± 2.2	5.4 ± 3.3	<.001
Neonatal outcomes			
Death, %	14	3	<.001
BPD, %	51	53	
BPD or death, %	57	55	
Home O_2, %	32	24	
Home O_2 or death, %	41	27	.005
ROP treated, %	18	20	

BPD or death, BPD or death before 36 wk; *Death*, death any time during the neonatal hospitalization; *Home O_2 or death*, infant died before hospital discharge or required supplemental oxygen when discharged; *Late bacteremia*, culture-positive bacteremia that was not associated with NEC or GI perforation; *NEC or GI perforation*, necrotizing enterocolitis (Bell classification II or greater[3]) or spontaneous gastrointestinal perforation; *ROP*, retinopathy of prematurity requiring laser or bevacizumab treatment; *Small for gestation*, birth weight-for-gestational-age z scores were obtained using the growth curves from Fenton et al.[2]

Values in the table are percentages, mean ± SDs, or median (IQR).

**P* values are presented only for values < .150.

As a group, the infants who were treated outside the trial due to LPE were treated at an earlier postnatal age and had earlier ductus constriction than infants enrolled in PDA-TOLERATE (Table I). Because recent controlled quality improvement projects[4-6] and controlled observational studies[7] have reported that early PDA constriction and early PDA treatment (before day 6) are associated with a lower incidence of late neonatal respiratory morbidity, we examined the infants who were treated outside the trial to see whether infants treated before postnatal day 6 had a lower incidence of late morbidity than infants treated ≥day 6 (Table II). Infants whose PDAs were treated before day 6 were born at a younger gestational age than those who were treated at ≥6 days (Table II). After adjusting for differences in gestational age and other demographic variables that have been associated with late neonatal respiratory morbidity (see Methods), we found that infants who were treated before day 6 had a significantly lower incidence of BPD (OR 0.277; 95% CI 0.113-0.681), combined outcome BPD or death (OR 0.256; 95% CI 0.105-0.625), and combined outcome needing home oxygen or death (OR 0.220; 95% CI 0.087-0.560) (Table III; available at www.jpeds.com).

Discussion

We found that eligible infants who were not enrolled in PDA-TOLERATE due to LPE were less mature and needed more respiratory support than infants who were enrolled in the trial (Table I). However, infants with LPE (who were treated outside the trial) had a similar or significantly lower incidence of late neonatal morbidity and mortality compared with enrolled infants despite their relative immaturity and their greater need for respiratory support

Table II. Comparison of prenatal and neonatal characteristics of infants not enrolled in the PDA-TOLERATE trial (due to the medical team's preference for PDA treatment) who were treated either ≤ day 5 or ≥ day 6

	Infants NOT enrolled due to physician preference		
Characteristics	**Treated ≥ day 6 (n = 52)**	**Treated ≤ day 5 (n = 85)**	***P* value***
Prenatal variables			
Maternal age, y, mean ± SD	28.1 ± 5.7	29.0 ± 6.2	
Multiple gestation, %	35	36	
Premature rupture of membranes, %	26	18	
Preeclampsia, %	22	18	
Chorioamnionitis, %	10	17	
Diabetes, %	4	9	
Cesarean delivery, %	69	80	
Betamethasone ≥24 h, %	58	49	
Neonatal variables			
Gestation, wk, mean ± SD	25.8 ± 1.2	25.3 ± 1.2	.021
Gestation ≤25 wk, %	48	69	.013
Birth weight, g, mean ± SD	824 ± 177	762 ± 177	.049
Small for gestational age, %	4	12	.112
Male, %	48	46	
White, %	46	28	.033
Apgar (10-min) ≥6, %	92	98	.138
Surfactant, %	96	98	
Dopamine during first 72 h after birth, %	14	26	.094
Intubated in delivery room, %	81	87	
Intubated at 24 h, %	73	74	
Intubated at 8 d, %	63	63	
Intubated at 15 d, %%	54	68	.091
Postnatal steroids, %	44	51	
Early-onset bacteremia, %	0	6	.075
Late bacteremia, %	10	24	.038
NEC or GI perforation, %	8	21	.035
Age when ductus constricted (small or closed), d, median (IQR)	16 (11-16)	8 (6-19)	<.001
Age at decision to treat PDA, d, mean ± SD	8.8 ± 2.8	3.3 ± 1.2	<.001
Neonatal outcomes			
Death, %	6	1	.125
BPD, %	63	48	.114
BPD or death, %	65	49	.072
Home O_2, %	34	19	.048
Home O_2 or death, %	38	20	.020
ROP treated, %	13	23	

Values in the table are percentages, mean ± SD, or median (IQR).
**P* values are presented only for values < .150.

(Table I). We hypothesize that this paradoxical finding could be due to the earlier PDA treatment and ductus constriction that occurred in infants who were treated outside of the trial (Table I). Recent controlled quality improvement studies[4-6] and epidemiologic studies[8,9] have reported an association between early PDA treatment and lower rates of BPD and neonatal morbidity. In our study, infants who were treated outside the trial, before day 6, had a lower incidence of late neonatal respiratory morbidity than infants who were treated after day 6 (Table III). This occurred despite the fact that infants who were treated before day 6 were less mature and had more complications (eg, bacteremia and necrotizing enterocolitis) than infants who were treated after day 6 (Table II).

Our study has several limitations. The study coordinators were aware of the treatments the infants received. This may have affected some of the study outcomes. Data were unavailable for infants who were treated outside of the study from 1 of the 17 study sites, although that site only contributed 2 infants to the parent PDA-TOLERATE trial. In addition, the relatively small number of infants in each of the study groups also may have limited the overall power of our analyses. Last, unmeasured differences between the groups, which could have affected the outcomes, may have existed despite the fact that infants enrolled in PDA-TOLERATE and infants treated outside the trial were admitted concurrently and met the same eligibility criteria. For example, infants enrolled in the trial needed both physician and parental consent to enter the trial (22% of the families declined to enroll their infants). Because the parents of infants who were treated outside of the trial were never given the opportunity to decline trial entry, the number of infants included in the LPE group may be spuriously elevated. The absence of a parental declination step in the LPE group also may have altered the demographic composition of the group, as evidenced by the greater number of nonwhite infants in that group.[10]

Although the timing of PDA treatment appears to influence neonatal outcomes in our study, it does not necessarily mean that earlier PDA treatment leads to less morbidity. The study was not primarily designed to evaluate the effects of

treatment before and after 6 days; and, even though we adjusted our analyses for demographic variables that differed between the 2 "time-of-treatment" subgroups (**Table II** and **Table III**), there may have been unmeasured infant characteristics that led physicians to think that infants treated early were more "PDA-compromised" than those treated late. Our findings underscore the need for appropriate randomized controlled trials specifically designed to examine the benefits or risks of PDA treatment initiated shortly after birth compared with conservative approaches that delay PDA treatment beyond the first week. ■

Submitted for publication Mar 15, 2019; last revision received Apr 16, 2019; accepted May 20, 2019.

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Data statement

Data sharing statement available at www.jpeds.com.

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Table III. Neonatal outcomes among infants who were not enrolled in the PDA-TOLERATE trial and received open-label PDA treatment due to physician preference: a comparison of the effects of PDA treatment on or before day 5 with treatment on or after day 6

	Multivariable models (effects of PDA treatment ≤ day 5 compared with treatment ≥ day 6*)	
Outcomes	**OR (95% CI)†**	***P* value**
Death	0.082 (0.005-1.393)	.083
BPD	0.277 (0.113-0.681)	.005
BPD or death	0.256 (0.105-0.625)	.003
Home O_2 or death	0.220 (0.087-0.560)	.001

*Multivariate models were designed to compare the effects of PDA treatment before day 6 with treatment on or after day 6 on neonatal outcomes (see the Methods). Variables included in the final models:

Death: postnatal age at treatment, gestational age, betamethasone ≥24 h, small for gestational age, dopamine during first 72 hours after birth, and white race.

BPD: postnatal age at treatment, gestational age, betamethasone ≥24 h, and small for gestational age.

BPD and death: postnatal age at treatment, gestational age, betamethasone ≥24 h, and small for gestational age.

Home O_2 or death: postnatal age at treatment, gestational age, betamethasone ≥24 h, and small for gestational age.

†OR and 95% CI of PDA treatment ≤ postnatal day 5 compared with treatment ≥ day 6.