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ARTICLE

Comparative effectiveness of drugs used to constrict the patent ductus arteriosus: a secondary analysis of the PDA-TOLERATE trial (NCT01958320)

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Abstract

Objective To evaluate the effectiveness of drugs used to constrict patent ductus arteriosus (PDA) in newborns < 28 weeks.

Methods We performed a secondary analysis of the multi-center PDA-TOLERATE trial (NCT01958320). Infants with moderate-to-large PDAs were randomized 1:1 at 8.1 ± 2.1 days to either Drug treatment ($n = 104$) or Conservative management ($n = 98$). Drug treatments were assigned by center rather than within center (acetaminophen: 5 centers, 27 infants; ibuprofen: 7 centers, 38 infants; indomethacin: 7 centers, 39 infants).

Results Indomethacin produced the greatest constriction (compared with spontaneous constriction during Conservative management): RR (95% CI) = 3.21 (2.05–5.01)), followed by ibuprofen = 2.03 (1.05–3.91), and acetaminophen = 1.33 (0.55–3.24). The initial rate of acetaminophen-induced constriction was 27%. Infants with persistent moderate-to-large PDA after acetaminophen were treated with indomethacin. The final rate of constriction after acetaminophen ± indomethacin was 60% (similar to the rate in infants receiving indomethacin-alone (62%)).

Conclusion Indomethacin was more effective than acetaminophen in producing ductus constriction.

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Introduction

Most preterm infants ≥ 28 weeks of gestation close their patent ductus arteriosus (PDA) spontaneously by the end of the first postnatal week [1, 2]. In contrast, 50–70% of infants < 28 weeks of gestation, have a moderate-to-large PDA shunt that persists for weeks after birth [3]. Indomethacin and ibuprofen are currently the only labeled drugs to promote constriction of the PDA. In 2011, Hammerman et al reported that acetaminophen was an effective drug for constricting the PDA in preterm infants [4]. The presumed mechanism of action was decreased prostaglandin production within the ductus wall through competitive inhibition of the peroxidase component of prostaglandin endoperoxide H2 synthase [5, 6].

Acetaminophen (with its presumed superior safety profile) has the potential to be an excellent substitute for the two currently labeled drugs if its efficacy can be shown to be comparable. To date, acetaminophen has been examined in 10 published randomized clinical trials (RCTs). These RCTs and subsequent meta-analyses suggest that acetaminophen's efficacy is comparable to the efficacy of indomethacin and ibuprofen [7–19]. Unfortunately, only one of the 10 RCTs [10] exclusively enrolled infants that were at high risk for having a persistent PDA – namely, those born before 28 weeks of gestation. The 9 RCTs that included infants born ≥ 28 weeks of gestation (where the PDA was likely to close spontaneously by the end of the first week [1, 2]) ran the risk of biasing the PDA outcome towards the null hypothesis when comparing acetaminophen with indomethacin or ibuprofen. Therefore, we designed the following study, in infants born before 28 weeks of gestation, to determine if acetaminophen was as effective as indomethacin in constricting the PDA.

The PDA-TOLERATE trial (NCT01958320, Clinicaltrials.gov) was a RCT designed to determine if routine use of drugs to promote closure of moderate-to-large PDAs, that were still present at the end of the first week in infants born below 28 weeks of gestation, would reduce neonatal morbidity compared with a Conservative approach that delayed PDA drug use for at least another 7–10 days [20]. Infants in the PDA-TOLERATE trial were randomized to either routine Early drug treatment to constrict the PDA (where they received either acetaminophen, ibuprofen, or indomethacin as their initial drug treatment) or to Conservative treatment. We performed the following secondary analysis of the PDA-TOLERATE trial [20] to compare the rates of PDA constriction in infants < 28 weeks of gestation who received either no treatment (the Conservative group) or received treatment with indomethacin, ibuprofen or acetaminophen. Our goal was to determine if acetaminophen was as effective as indomethacin in constricting the PDA. Since recent studies have shown that the only PDA shunts that are associated with neonatal morbidity are moderate-to-large shunts, ("smal PDA shunts" do not appear to have any association with morbidity [21, 22]), we tested the hypothesis that acetaminophen was as effective as indomethacin in producing "successful ductus constriction" by eliminating the presence of moderate-to-large PDA shunts (see Statistical analysis below for definition of "successful ductus constriction").

Methods

Our study utilized data from the 202 patients enrolled in the PDA-TOLERATE trial (NCT01958320), a prospective randomized controlled trial conducted between January 2014 and June 2017 at 17 international sites to compare the effects of Early Routine treatment of moderate-to-large PDAs with a Conservative approach that delayed treatment to promote constriction of the PDA until prespecified respiratory and hemodynamic "Rescue" criteria were met. Full details of the PDA-TOLERATE trial including screening, echocardiographic analyses, and enrollment have been published elsewhere [20]. Institutional review board approval and written informed parental consent were obtained before patient enrollment. All procedures followed were in accordance with the ethical standards of the institutional review boards.

Infants < 28 weeks of gestation were enrolled in the PDA-TOLERATE trial if they were between 6–14 days old, had a moderate-to-large PDA (see Echocardiographic studies), and were receiving greater than minimal respiratory support [20]. Eligible infants were excluded from participation if they had received prior treatment with indomethacin or ibuprofen, had chromosomal anomalies, congenital or acquired gastrointestinal anomalies, prior episodes of necrotizing enterocolitis or intestinal perforation, active pulmonary hemorrhage at the time of enrollment, or contraindications to the use of indomethacin or ibuprofen (e.g., hydrocortisone or dexamethasone administration within preceding 24 h, urine output < 1 ml/kg/h during preceding 8 h, 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 [20].

Echocardiographic studies in the PDA-TOLERATE trial were performed according to the study protocol and schedule for exams [20] and included two-dimensional imaging, M-mode, color flow mapping and Doppler interrogation as previously described [23, 24]. A moderate-to-large PDA was defined by a ductus internal diameter ≥ 1.5 mm (or PDA:left pulmonary artery diameter ratio ≥ 0.5) and one or more of the following echocardiographic criteria: (a) left

atrium-to-aortic root (LA/Ao) ratio ≥ 1.6, (b) ductus flow velocity ≤ 2.5 m/s or mean pressure gradient across the ductus ≤ 8 mm Hg, (c) left pulmonary artery diastolic flow velocity > 0.2 m/sec, and/or d) reversed diastolic flow in the descending aorta. Ductus that did not meet these criteria were considered to be "*constricted*" (small or closed) and not eligible for enrollment or treatment.

Enrolled infants ($n = 202$) were randomized to one of two groups: Early drug use to promote PDA constriction ($n = 104$) or a Conservative approach ($n = 98$) that delayed drug use until prespecified respiratory and hemodynamic "Rescue" criteria were met. Randomization was stratified by gestational age ($23^{0/7}$–$25^{6/7}$ or $26^{0/7}$–$27^{6/7}$) and by center. Block randomization at a 1:1 ratio occurred at each site. Study randomization was blinded, but treatment allocation by the medical team was not blinded because treatment blinding would have required unnecessary clinical procedures and blood sampling for infants in the Conservative group. The cardiologists or echocardiography-trained neonatologists reading the echocardiograms were unaware of the infants' treatment assignments.

Infants randomized to the Conservative group ($n = 98$) were not eligible for drug treatment to promote PDA constriction until at least 7 days after randomization and required one or more of the prespecified "Rescue" criteria before Rescue treatment could be given (see Rescue criteria below).

Infants randomized to the Early drug treatment group ($n = 104$) received one of three drug treatment protocols. We anticipated that there would be limited patient enrollment at each study center and felt that it was unlikely that a within-center randomization scheme would insure equal distribution of the three drugs among the enrollees at each of the study centers. Therefore, drug treatments were assigned by center rather than within center, and the relative effectiveness of each drug was determined by comparing its effectiveness with reference to spontaneous closure. One drug treatment protocol was used at each site (one site used each of the three protocols during three sequential study periods). The acetaminophen protocol was used at 5 centers, the ibuprofen protocol at 7 centers, and the indomethacin protocol at 7 centers.

Initial drug treatment protocols for the Early treatment group were:

Acetaminophen protocol: 20 mg/kg acetaminophen loading dose followed by a maintenance dose of 12.5 mg/kg every 6 h for 19 maintenance doses (over 5 days). Acetaminophen was administered either enterally (3 infants) or intravenously (24 infants). A "trough" acetaminophen concentration was obtained 30 min before the 3rd maintenance dose. If the concentration was <15 mg/L, the subsequent maintenance doses were increased to 15 mg/kg and a "trough" acetaminophen concentration was obtained before the 3rd new maintenance dose. Twenty-five of the 27 infants required 15 mg/kg for maintenance doses 4–19. An echocardiogram was performed 24–48 h after completing the initial acetaminophen treatment course. If the PDA was still moderate-to-large after the initial acetaminophen course the infant was treated with indomethacin as a backup Early drug treatment (see indomethacin protocol).

Ibuprofen protocol: 10 mg/kg ibuprofen loading dose followed by a maintenance dose of 5 mg/kg every 24 h for up to 4 maintenance doses (4 infants received 20 mg/kg loading and 10 mg/kg maintenance doses). Ibuprofen was administered either enterally (14 infants) or intravenously (24 infants). Three of the seven ibuprofen centers administered the intravenous acetaminophen protocol simultaneously with the ibuprofen protocol. The results from infants who received acetaminophen and ibuprofen simultaneously were grouped together for analysis with the results from infants who received ibuprofen alone since a recent pilot study was unable to detect a difference in PDA closure when intravenous acetaminophen and ibuprofen were administered simultaneously [25]. An echocardiogram was performed 24–48 h after completing the initial ibuprofen treatment course. If the PDA was still moderate-to-large after the initial ibuprofen course the infant could be treated with indomethacin as a backup Early drug treatment (see indomethacin protocol).

Indomethacin protocol: 0.2 mg/kg indomethacin intravenous doses at 0, 12, 24, 48 h (4 doses). An echocardiogram was performed within 24 h after the 4th dose. If the ductus was still open, doses 5 and 6 were administered at 72 h and 96 h and a repeat echocardiogram was performed 24–48 h after completing the last dose of indomethacin.

Seven-to-ten days after randomization, a repeat echocardiogram was performed on all infants in both the Conservative and Early treatment groups. Infants with a "constricted" (small or closed) 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 h. In addition, routine echocardiograms were performed every 2–3 weeks until ductus closure or hospital discharge in infants with a "constricted" PDA. Infants with a persistent moderate-to-large PDA after the first week were followed with frequent (every 7–14 days) echocardiograms to determine when ductus constriction occurred. Echocardiograms were performed until ductus closure or hospital discharge.

Infants in the Conservative group, with a persistent moderate-to-large PDA after the first week, were eligible for rescue drug treatment to promote PDA constriction if they met one or more prespecified "Rescue" criteria, which included: inotrope-dependent hypotension that required continuous dopamine support for at least 3 days (with

hypotension defined as mean blood pressure at least 2–3 mmHg below the infant's postmenstrual age), or oliguria (<2 ml/kg/hour) that persisted for at least 2 days (with no obvious cause, other than the moderate PDA, to explain the condition), or respiratory support that surpassed pre-specified ventilation and FiO2 requirements (see reference [20] for criteria). The "Rescue" drug protocol at a site was the same drug protocol used for the "Early treatment" group at that site. Neonatologists caring for infants in the Conservative group were not required or encouraged to treat infants who met "Rescue" criteria. Rather, the "Rescue" criteria served as the threshold or minimal criteria that were needed before infants in the Conservative group could be eligible for closure treatment. Infants in the Early treatment group, with persistent moderate-to-large PDAs after the first week, could receive rescue treatment at the clinician's judgment, whether or not they met "Rescue" criteria.

"Trough" serum acetaminophen concentrations were measured by a turbidimetric inhibition immunoassay performed on a Beckman DxC 800 instrument (Beckman Coulter, Inc.) in the hospitals' clinical laboratories.

A Data Safety Monitoring Board performed regular interim analyses and reviewed all serious adverse events (see reference [20]).

Statistical analysis

Our study's primary goal was to compare the incidence of "successful spontaneous ductus constriction", at 7–10 days after enrollment in the Conservative group, with the incidence of "successful ductus constriction" after the initial acetaminophen, ibuprofen, or indomethacin treatments (prior to the use of any backup drug treatment with indomethacin). "Successful ductus constriction" was defined as ductus that were small or closed on the echocardiogram performed after the initial drug protocol (or at 7–10 days after enrollment in the Conservative group). Ductus that were initially small or closed after treatment (or at 7 days after enrollment in the Conservative group) but later reopened and became moderate-to-large again were not considered to have achieved "successful constriction".

All analyses were performed with the statistical software STATA (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). Chi-Squared tests were used to compare the treatment groups for categorical variables. For continuous variables, analysis of variance was used to compare groups for parametric variables and Kruskal-Wallis equality-of-populations rank test to compare groups for non-parametric variables. Generalized estimating equations were used to model the relationship between the initial drug or Conservative management and the response to treatment adjusted for potential confounders. Based on previous studies [26–32] showing an association between initial ductus closure and gestational age, antenatal betamethasone exposure and race, we decided a priori to include these variables in the model. We specified a Poisson distribution so that we could directly estimate relative risks from this model. Since the type of drug received was highly correlated to the study site, we adjusted standard errors of the model for clustering by study site. We specified an exchangeable correlation and used robust standard errors. STATA's contrast command was used to perform a test of trend across the categories of initial drug protocols to determine if there was a significant linear trend.

Results

Our goal was to determine the incidence of "successful ductus constriction" after Conservative treatment (spontaneous constriction at 7–10 days) or after initial drug treatment with acetaminophen, ibuprofen, or indomethacin. Two-hundred and two infants were enrolled in the PDA-TOLERATE trial and randomized between Conservative treatment ($n = 98$) and Early treatment ($n = 104$) approaches. Early drug treatment protocols were assigned by center and the relative effectiveness of each drug was determined by comparing its effectiveness with reference to spontaneous constriction. The acetaminophen protocol was used at 5 centers (27 infants), the ibuprofen protocol at 7 centers (38 infants), and the indomethacin protocol at 7 centers (39 infants) (Fig. 1). Six infants died before drug treatment and echocardiographic analysis could be completed (Fig. 1). Prenatal and neonatal demographic characteristics were similarly distributed among the 196 surviving infants in the Conservative and Early treatment study groups except for the incidences of Caucasian race and early onset bacteremia (Table 1).

The frequencies of spontaneous or initial drug-induced constriction are shown in Fig. 1. In this population of infants delivered before 28 weeks of gestation, who still had a moderate-to-large PDA at the end of the first week, only 20% constricted their ductus spontaneously during the next 7–10 days (Fig. 1). After adjusting for gestational age, antenatal betamethasone exposure and Caucasian race, we found a significant ($p = 0.001$) linear test of trend for the rate of ductus constriction among the study groups with indomethacin having the greatest effectiveness for ductus constriction (relative risk compared with Conservative treatment (RR, (95% CI) = 3.21, (2.05–5.01)), followed by ibuprofen (2.03, (1.05–3.91)) and acetaminophen (1.33, (0.55–3.24)) (Table 2).

In our study acetaminophen produced a non-significant increase in the rate of constriction compared with the rate of spontaneous constriction after Conservative treatment. There was no significant difference in the "trough"

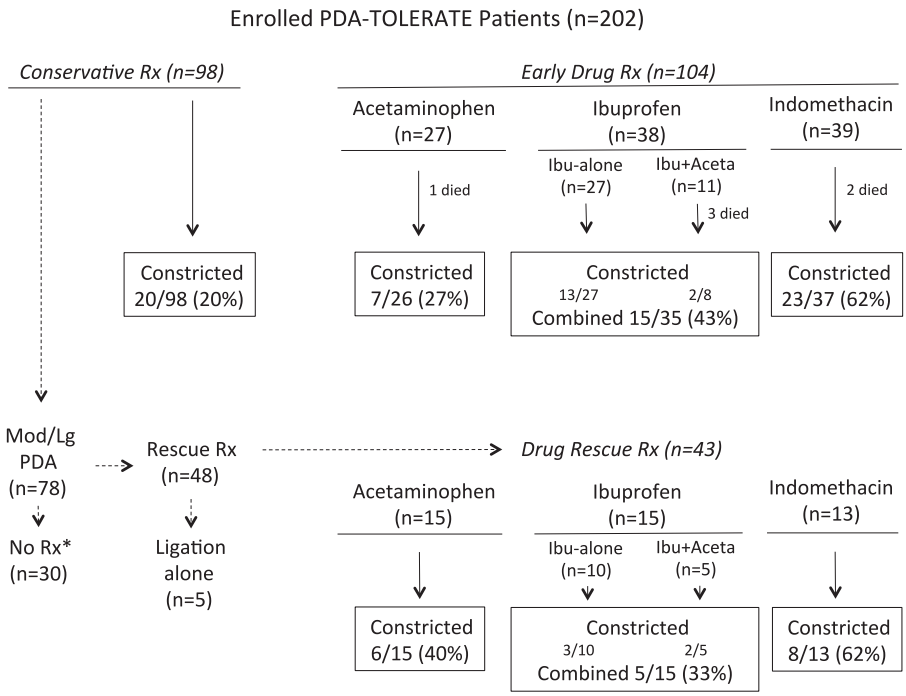

Fig. 1 Flow diagram of patient distribution and ductus outcomes among Conservative management and Drug treatment groups. No Rx*: Thirty infants with a moderate-to-large PDA did not receive rescue treatment because they either did not meet the Rescue clinical criteria ($n = 17$) or the clinical team chose not to treat them despite having met Rescue criteria ($n = 13$) (see Methods). 26/30 (87%) constricted their ductus spontaneously by the time of discharge from the hospital. Note: among the 38 infants treated with Early Rx Ibuprofen 34 received a loading dose of 10 mg/kg followed by maintenance doses of 5 mg/kg. Four infants received 20 mg/kg loading and 10 mg/kg maintenance doses. Only one of the four (25%) infants in the high dose group had successful ductus constriction

acetaminophen concentrations (after the highest dose of acetaminophen) between infants with a constricted ductus (mean ± sd: 16.1 ± 3.2 mg/L; range: 12–21) and those with a persistent moderate-to-large PDA (15.5 ± 3.7 mg/L; range: 10–22). The "trough" acetaminophen concentrations also were similar after intravenous and enteral acetaminophen administration (intravenous (n = 23): 15.7 ± 3.4 mg/L; range (10–22), enteral (n = 3): 15.7 ± 4.7 mg/L; range (14–21)). Infants who were treated initially with acetaminophen and still had a persistent moderate-to-large PDA after treatment were subsequently treated with indomethacin (see acetaminophen protocol, Methods). The final rate of constriction in the acetaminophen group (after either successful constriction with acetaminophen-alone or after the combination of acetaminophen followed by indomethacin) was 60%.

Forty-three infants in the Conservative treatment group received Rescue drug treatment to promote PDA closure at 21 ± 8 days postnatal age. The rates of ductus constriction after Rescue drug treatment were similar to the rates of constriction after Early Drug treatment (Fig. 1). "Trough" acetaminophen concentrations after Rescue acetaminophen treatment were similar in infants with a constricted ductus (mean ± sd: 17.0 ± 4.3 mg/L; range: 10–21) and those with a persistent moderate-to-large PDA (19.5 ± 5.0 mg/L; range: 13–29). The "trough" acetaminophen concentrations also were similar after Rescue intravenous and Rescue enteral acetaminophen administration (intravenous (n = 10): 17.7 ± 5.4 mg/L; range (10–29), enteral (n = 5): 20.5 ± 2.1 mg/L; range (18–23)), as were the rates of ductus constriction (intravenous: 40%; enteral: 40%). The overall rate of ductus constriction after either Early drug treatment or Rescue drug treatment was significantly higher for indomethacin (31/50 (62%)) when compared with either ibuprofen (20/50 (40%), $p < 0.05$) or acetaminophen (13/41 (32%), $p < 0.01$).

Discussion

In our multi-center RCT the rate of spontaneous ductus constriction, among babies delivered before 28 weeks of gestation, who still had a moderate-to-large PDA at the end of the first week, was only 20% during the 7–10 days after enrollment. During the same time interval indomethacin treatment was associated with the greatest rate of constriction (62%), whereas acetaminophen was associated with the lowest rate (27%). Although our findings are consistent with previous preclinical in vitro [6] and in vivo [33, 34] studies they differ from the 10 previously published RCTs that consistently found acetaminophen to be as effective as

Table 1 Baseline demographic and clinical characteristics of babies in the Conservative and Early Drug Treatment groups

	Conservative ($n = 98$)	Early Treatment ($n = 98$)			p value[a]
		Acetaminophen ($n = 26$)	Ibuprofen ($n = 35$)	Indomethacin ($n = 37$)	
Prenatal variables:					
Maternal age (years (m ± sd))	29.9 ± 6.4	28.3 ± 5.9	28.7 ± 6.2	29.3 ± 6.6	
Multiple gestation (%)	39	27	17	24	0.075
Premature rupture of membranes (%)	20	23	20	16	
Preeclampsia (%)	19	15	11	8	
Chorioamnionitis (%)	16	15	14	14	
Diabetes (%)	7	4	0	0	
Caesarian section (%)	70	62	60	78	
Betamethasone ≥ 24 h (%)	64	65	60	65	
Neonatal variables prior to enrollment:					
Gestation (weeks (m ± sd))	25.9 ± 1.1	25.6 ± 1.5	25.6 ± 1.2	25.9 ± 1.1	
Gestation ≤ $25^{6/7}$ weeks (%)	52	53.9	51.4	56.8	
Birthweight (grams (m ± sd))	810 ± 179	778 ± 176	809 ± 170	777 ± 140	
Small for Gestation (%)	9	4	9	3	
Male (%)	44	50	49	43	
Caucasian (%)	55	50	69	32	0.019
Apgar (5-min) ≤ 5 (%)	28	31	20	32	
Apgar (10-min) ≤ 5 (%)	7	8	11	5	
Delivery room intubation (%)	71	65	74	62	
Intubated at 24 h (%)	70	54	60	59	
Intubated at enrollment (%)	48	54	40	59	
Surfactant (%)	94	92	91	84	
Dopamine prior to enrollment (%)	35	23	35	41	
Dopamine at enrollment (%)	6	4	6	8	
Pulmonary Hemorrhage prior to enrollment (%)	3	12	3	3	
Early onset bacteremia (≤ 3 days) (%)	0	0	6	11	0.007
sIVH prior to enrollment (%)	11	12	26	16	
Age at enrollment (days (m ± sd))	8.3 ± 2.3	8.0 ± 2.4	7.6 ± 1.8	8.5 ± 2.2	

Pulmonary hemorrhage was defined as: gross blood in the endotracheal tube, new infiltrates on the chest radiograph, and deterioration in infant's respiratory status

[a]p value are presented only for values ≤ 0.10

indomethacin and ibuprofen in constricting the ductus [7–19].

Our study design differed from the prior RCTs in several respects. Although the centers in our study randomized Early drug treatment and Conservative management in a 1:1 ratio, only one of the three drug treatment protocols was used at each center. Therefore, we determined the relative effectiveness of the different drug treatments by comparing their effectiveness with reference to spontaneous closure. We think it is unlikely that centers using acetaminophen had a lower rate of responsiveness to prostaglandin synthase inhibitors than centers using indomethacin. As part of the acetaminophen protocol, infants whose PDA failed to constrict after acetaminophen treatment were subsequently treated with indomethacin and their combined rate of acetaminophen ± indomethacin constriction was 60% (which was similar to the rate of ductus constriction at centers that used indomethacin-alone (62%)).

Our study exclusively enrolled infants < 28 weeks of gestation. In contrast, only one of the prior RCTs [10] enrolled infants that were exclusively below 28 weeks of gestation. The remaining studies enrolled more mature infants. The effectiveness of drugs that promote ductus constriction depends on the infant's developmental age at the time of treatment [32]. Therefore, some of the different outcomes between our trial and the prior trials may be due to the different developmental ages of the study populations.

Table 2 Adjusted relative risk and 95% confidence interval of the relationships between the individual treatment groups and ductus constriction

	Relative Risk	95% CI	*p* value[a]
Treatment group			
Conservative	1.0		
Acetaminophen	1.33	(0.55–3.24)	
Ibuprofen	2.03	(1.05–3.91)	0.035
Indomethacin	3.21	(2.05–5.01)	< 0.001
Gestation $<26^{0/7}$ weeks	1.0		
Gestation $\geq 26^{0/7}$ weeks	1.21	(0.85–1.70)	
Betamethasone <24 h	1.0		
Betamethasone ≥ 24 h	0.78	(0.58–1.05)	
Caucasian -no	1.0		
Caucasian -yes	1.14	(0.75–1.74)	

The potential confounders in the model were: gestational age ($<26^{0/7}$ weeks or $\geq 26^{0/7}$ weeks), antenatal betamethasone exposure (<24 h or ≥ 24 h), and Caucasian race (yes or no)

[a]*p*-value are presented only for values ≤ 0.10

Although the final acetaminophen dosing schedule in our trial was similar to the one used in prior RCTs, the route of acetaminophen administration differed significantly between our trial and the previous trials (88% received intravenous dosing in our trial; 80% received enteral dosing in the prior RCTs). To date, only two small trials have compared the effects of intravenous and enteral acetaminophen administration on ductus constriction and reported opposing results [6, 35]. In our study, there were no differences in "trough" acetaminophen concentrations or rates of ductus constriction between the two routes of administration.

Recently Bin-Nun et al. [36], using a similar acetaminophen dosing schedule as ours, reported that serum acetaminophen concentrations (measured 4 h after an enteral dose) predicted the ductus' contractile response to treatment. They reported that acetaminophen concentrations ≥ 20 mg/L were needed to produce ductus constriction. Although we used a similar dosing schedule as Bin-Nun et al, we found lower trough acetaminophen concentrations. The average "trough" acetaminophen concentrations in our study were 16.6 ± 4.1 mg/L (range: 10–29) (measured 5.5 h after an enteral or intravenous dose). We also found no differences in the "trough" acetaminophen concentrations between infants who constricted their ductus and those who did not. Future pharmacodynamics trials will be needed to determine if serum acetaminophen concentrations can predict ductus constriction and whether these concentrations can be achieved safely by increasing enteral or intravenous dosing.

Our trial had several limitations. We anticipated that there would be limited enrollment at each study center and felt that it was unlikely that a within-center randomization scheme would insure equal distribution of the three drugs among the enrollees at each of the study centers. Therefore, drug treatments to promote PDA closure were assigned by center rather than within center, and the relative effectiveness of each drug was determined by comparing its effectiveness with reference to spontaneous closure. This limited our ability to compare one drug treatment directly with another. The relatively small number of infants in each of the drug treatment groups also limited the overall power of our analysis. Although both the study treatment randomization (to Early or Conservative treatment) and the reading of the study echocardiograms were performed in a blinded manner, the medical teams were aware of the treatments that infants received which may have affected some of the other study outcomes. The PDA-TOLERATE trial allowed for backup indomethacin therapy and Rescue drug treatment when the initial drug treatment failed to constrict the ductus: 44% of the Conservative group received Rescue drug treatment to promote PDA closure and 37% of the Early drug treatment group received backup drugs that differed from the initial drugs they were treated with. This made it impossible to evaluate potential morbidities that might be due solely to the Conservative management or the initial drug treatments.

In addition to our findings related to the effectiveness of different drug treatment protocols, we made several other observations that may add to our understanding of drug treatment to promote PDA constriction. Prior studies have shown that an infant's gestational age, race, and prior exposure to betamethasone play a significant role in determining the rate of drug-induced closure during the first days after birth [26–32]. In the current study, we found that these risk factors no longer play a role in the rate of ductus constriction when treatment is started after the first week (Table 2). Similarly, while drug efficacy appears to decline during the course of the first postnatal week [37, 38], beyond the first week any additional decline in drug potency appears to be much less noticeable. We found that the rates of ductus constriction after routine drug treatment at 8.1 ± 2.1 days were similar to the rates after Rescue drug treatment at 21 ± 8 days (Fig. 1).

In conclusion, we found that acetaminophen was less effective than indomethacin when used as initial drug treatment at the end of the first week to produce ductus constriction in infants < 28 weeks of gestation. The current interest in acetaminophen for PDA constriction is based on the thought that if effective, acetaminophen might have fewer side effects than indomethacin or ibuprofen. Recently,

concern has been raised about acetaminophen's presumed superior safety profile based on reports of neurocognitive impairment after prenatal exposure [39]. Unfortunately, information about acetaminophen's long-term effects in this population is lacking. Since our study questions the relative efficacy of acetaminophen in producing ductus constriction, it underscores the need for appropriate pharmacodynamic and follow-up studies examining both the route and dose of acetaminophen before routine use can be recommended in this vulnerable population.

Data availability

After de-identification individual participant data that underlie the results reported in this article will be available to researchers who provide a methodologically sound proposal. Proposals should be directed to clymanr@ucsf.edu. To gain access, data requestors will need to sign a data access agreement.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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