

**RESEARCH LETTER**

# Intravenous acetaminophen vs intravenous ibuprofen to close a patent ductus arteriosus closure: A pilot randomized controlled trial

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## 1 | INTRODUCTION

Patent ductus arteriosus (PDA) is a common finding in preterm infants. Some PDAs will close spontaneously but those that remain open can be associated with significant morbidities and mortality.<sup>1-4</sup> The current standard of care to treat a hemodynamically significant PDA (hsPDA) is to use either intravenous (IV) ibuprofen or IV indomethacin. These medicines have a non-selective mechanism of COX inhibition which can lead to side effects.<sup>5-7</sup> To avoid this, researchers have explored using acetaminophen, which has COX-2 selectivity.<sup>8,9</sup> Recent studies using enteral acetaminophen for PDA closure have suggested that it is safe and effective.<sup>5,6,10,11</sup>

The diagnosis of a hsPDA is confirmed by echocardiogram which evaluates size of the PDA and stress on the heart. B-type natriuretic peptide (BNP) levels produced in the ventricles of the heart rise in response to stretch from volume overload and have been used in previous studies to help determine the efficacy of ibuprofen treatment for a hsPDA.<sup>12-14</sup> Studies evaluating the efficacy of enteral acetaminophen for PDA closure have not reported BNP levels.

The efficacy of intravenous acetaminophen for closure of a hsPDA is unknown. We developed a proof of concept study to assess whether IV acetaminophen can be effective at closing a hsPDA using echocardiogram and BNP data as outcome measures.

## 2 | METHODS

### 2.1 | Study design and treatment

Infants 23 0/7 weeks through 29 6/7 weeks at birth with a hsPDA diagnosed by echocardiogram within the first 2 weeks of life were recruited in the neonatal intensive care unit at the Bernard and Millie Duker Children's Hospital at Albany Medical Center in Albany, NY. Written parental consent was obtained prior to randomization. This study was approved by the Institutional Review Board and registered on clinicaltrials.gov (NCT03008876).

Five infants were randomized to each treatment group (10 infants total). The IV ibuprofen group received three doses: a loading dose of 10 mg/kg/dose on the first day followed by 5 mg/kg/dose on the second and third day. The IV acetaminophen group received 12 doses: 15 mg/kg/dose administered every 6 hours (total 3 days).

Infants with any of the following were excluded: sepsis and/or meningitis, necrotizing enterocolitis, intestinal perforation, major congenital heart disease, major congenital malformations or disorders, fetal hydrops, pulmonary hypertension, grade 3 or 4 intraventricular hemorrhage, evidence of acute renal injury, thrombocytopenia, prior treatment with a prostaglandin, or of their aspartate transaminase (AST) and alanine transaminase (ALT) levels were twice the upper limits of normal.

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## 2.2 | Primary outcome

The primary outcome was PDA closure. Echocardiograms were performed for initial diagnosis and then 1 day after study drug completion. The ductus was graded as large, moderate, small, or closed, taking into consideration the LA: Ao ratio, the ductal diameter, and the doppler flow pattern through the PDA.

## 2.3 | Secondary outcome

The secondary outcome was BNP level. BNP levels were obtained before and after treatment on the same day that the echocardiogram was performed and were not known to the medical team.

## 2.4 | Safety monitoring

Serum chemistries, complete blood count (CBC), AST/ALT, and bilirubin levels were performed before, during, and after the study drug was administered. If values were abnormal, the attending neonatologist could halt the medication administration.

## 2.5 | Statistical analysis

Group sizes were too small for statistical analysis of change in PDA size. BNP levels were analyzed using both a repeated measures ANOVA and Wilcoxon signed rank tests.

## 3 | RESULTS

Nineteen infants were eligible from January 2017 through May 2019. Ten infants were ultimately randomized after informed consent was obtained: five received IV acetaminophen and five received IV ibuprofen (Figure 1). Demographic characteristics were similar in each group (Table 1).

PDA closure was observed in two of the five infants in the IV acetaminophen group vs zero of five infants in the IV ibuprofen group. An additional infant in the IV acetaminophen group had a PDA that became smaller post study drug and then received two additional courses of IV ibuprofen. After the third course, the PDA was still present; however, it was closed on the echocardiogram prior to discharge. Of the remaining two infants in the IV acetaminophen group, one received two additional courses without improvement and

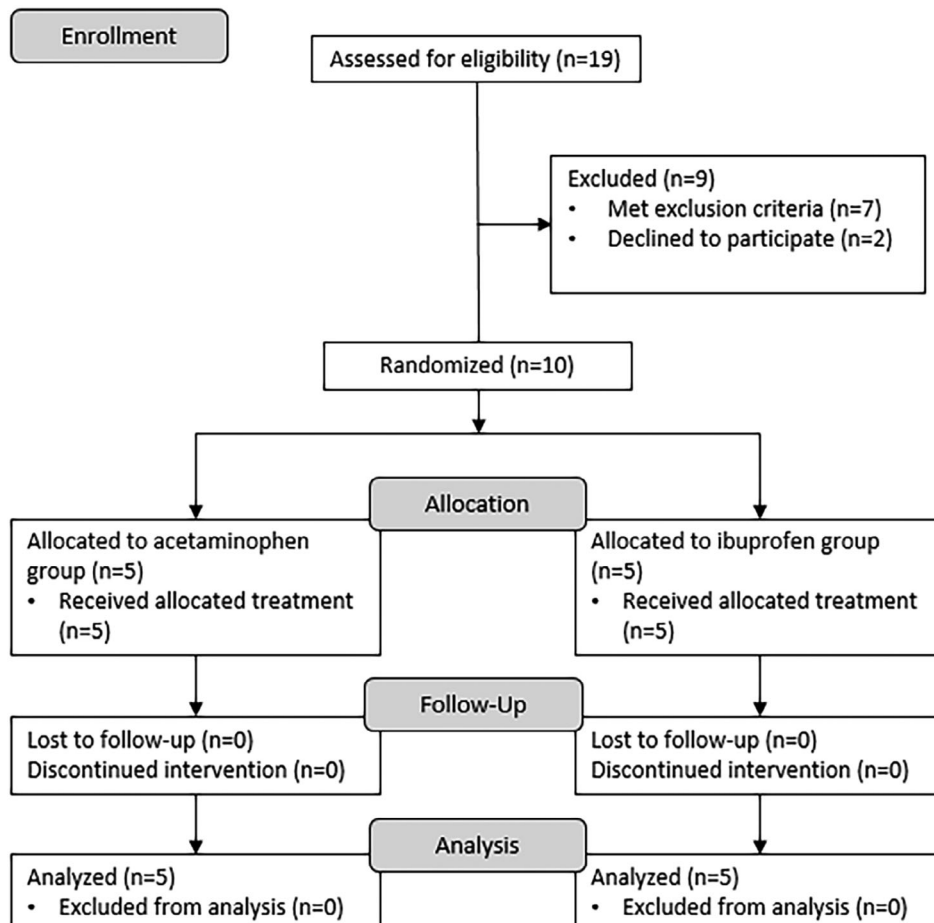


FIGURE 1 CONSORT diagram

**TABLE 1** Patient demographics

	Acetaminophen group N = 5	Ibuprofen group N = 5	P value
GA at birth (weeks)	26.2 ± 1.4	26.3 ± 2.3	.93
Sex (%male)	40	40	1
Birthweight (g)	736 ± 240	916 ± 300	.38
Delivered by C-section (N)	4	3	1
Antenatal corticosteroid exposure (N)	4	5	1
5 minutes APGAR	5 (4–7)	7 (4–8)	.6
Age at first dose study drug (days)	7 ± 3	8 ± 5	.8

Note: Continuous data presented at the mean (SD) and median (IQR).

Abbreviations: GA, gestational age; IQR, interquartile range.

**TABLE 2** Outcome of PDA in each study group

(a) IV acetaminophen group						
Patient ID	GA at birth (weeks)	Postnatal age at study drug start (days)	Change after study drug	Subsequent courses (IV)		Status at discharge (open/closed/ligated)
				Acet	Ibu	
1	27.9	4	None	–	2	Ligated
6	27.9	12	Closed	–	–	Closed
7	25.4	4	Closed	–	–	Closed
8	24.3	9	Smaller	–	2	Closed
10	27.9	8	None	–	–	Closed
(b) IV ibuprofen group						
Patient ID	GA at birth (weeks)	Postnatal age at study drug start (days)	Change after study drug	Subsequent courses (IV)		Status at discharge (open/closed/ligated)
				Acet	Ibu	
2	27.9	6	Smaller	1	1	Open
3	24.1	5	None	–	2	Open
4	29.6	12	None	1	2	Ligated
5	24.9	4	Smaller	1	1	Open
9	25.1	14	None	–	1	Open

Abbreviations: Acet, acetaminophen; GA, gestational age; Ibu, ibuprofen; IV, intravenous; PDA, patent ductus arteriosus.

underwent a PDA ligation, and the other infant did not undergo any additional treatment and the ductus was closed on a later echocardiogram (see Table 2).

In the IV ibuprofen group, two of the five infants were noted to have smaller PDAs after the initial course. However, all five infants received additional courses of medication. Three infants had two additional courses of treatment (two of those received one course each of IV acetaminophen and IV ibuprofen and the third infant received two courses of IV ibuprofen), one infant had three additional courses (two IV ibuprofen, one IV acetaminophen), and the last infant had one additional course (IV ibuprofen) (see Table 2).

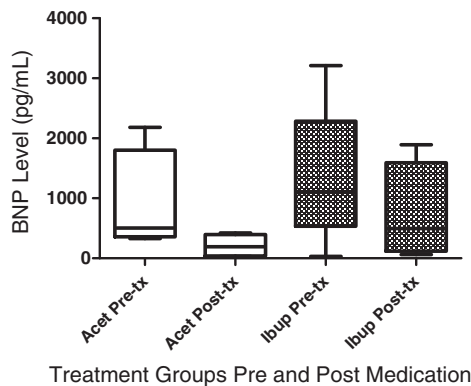
Five infants in the ibuprofen group and two in the acetaminophen group, required subsequent pharmacologic therapy. The hsPDA closure rate at discharge (not including those that underwent PDA

ligation), for infants in the IV acetaminophen group was higher compared to the IV ibuprofen group.

A repeated measures ANOVA analysis on BNP levels showed a significant decrease in BNP levels pre and post-treatment, regardless of the study group ( $P = .01$ ). There was a greater decrease in median BNP level after treatment in the IV acetaminophen group as compared to the IV ibuprofen group ( $P = .07$  vs  $P = .17$ , respectively) (Figure 2).

### 3.1 | Safety

Creatinine, AST/ALT, and fractionated bilirubin levels were all found to be within normal limits before, during, and after the study drug course in both groups. There were no cases of NEC or GI bleeding.



**FIGURE 2** Mean BNP level and SE of the mean for each study group pre and post medication administration. Acet, acetaminophen; BNP, B-type natriuretic peptide; Ibup, ibuprofen

## 4 | DISCUSSION

In this study the efficacy of acetaminophen in closing a PDA was evaluated. IV acetaminophen was used in our study, in comparison to many of the previous studies which used an enteral form, as we theorized a preterm infant's immature digestive system may alter enteral absorption and lead to lower serum concentrations and possible decreased efficacy in closing a PDA. Our results suggest that IV acetaminophen can successfully close a hsPDA. It was interesting to note that we saw no hsPDA closures from IV ibuprofen. The mean start day of treatment in this study was greater than previous studies which may explain lack of closure seen here as those infants who were treated earlier may have had a hsPDA that would have closed on its own. Since many are now using a watchful waiting approach to PDA management, the results in this study may be more reflective of the current outcomes with medical management.<sup>15</sup>

There was a decrease in cardiac stress (as measured by BNP level) in both groups, although greater in the acetaminophen group. To our knowledge, this is the first study to include BNP levels to assess the efficacy of acetaminophen on PDA closure. This study suggests that IV acetaminophen can be used as an alternative medication to close a hsPDA without adverse effects. The major limitation to this study was its small sample size and large scale studies are needed but will be challenging due to the current watchful waiting trend leading to decreased numbers of infants being treated. In addition to a larger number of patients, it would be useful to address the optimal dose and duration of IV acetaminophen for PDA closure as well as the long-term safety and potential effects on neurodevelopment. Bin-Nun et al<sup>16</sup> reported that a serum acetaminophen concentration > 20 mg/L was 100% sensitive and specific for ductal closure in their small cohort of preterm infants. However, McPherson et al<sup>17</sup> found no correlation between serum concentration and ductal size post-treatment.

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### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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All authors have read and approved the final version of this manuscript.

Kate A. Tauber had full access to all of the data in the study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

### TRANSPARENCY STATEMENT

Kate A. Tauber affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

### DATA AVAILABILITY STATEMENT

Deidentified data from this study will be shared following publication with those individuals who have approval from an institutional review board (IRB) from their institution and approval from the IRB at our institution. Persons requesting data will need to sign a data access agreement. If interested in obtaining the data from this study please contact tauberka@amc.edu.

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