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Late Acetaminophen Therapy for Patent Ductus Arteriosus in the Preterm Neonate

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OBJECTIVE In preterm infants, the standard pharmacologic treatment for a hemodynamically significant patent ductus arteriosus (hsPDA) is either ibuprofen or indomethacin. However, these medications may be less effective after 2 weeks of age. We investigated the use of acetaminophen in hsPDA closure beyond 2 weeks of age.

METHODS An observational study of 11 infants, <30 weeks' gestation at birth and postnatal age > 2 weeks, who received acetaminophen treatment for their hsPDA. Echocardiograms (ECHOs), B-type natriuretic peptide (BNP) levels, and the fraction of inspired oxygen (FiO_2) were obtained before and after treatment to analyze ductal characteristics. Renal and liver functions were monitored pretreatment and posttreatment to look for potential medication side effects.

RESULTS Of the 10 infants with ECHO data for before and after acetaminophen treatments, 4/10 (40%) had a decrease in PDA size, with no infants having complete closure immediately posttreatment. Eight of 11 (73%) infants had a decreased FiO_2 requirement after treatment. Of the 5 infants with pretreatment and posttreatment BNP data, 2/5 (40%) infants had a decrease in BNP level. One infant received an additional course of acetaminophen. Four infants underwent a surgical ligation. Two infants died. No medication side effects occurred with regard to hepatic and renal function.

CONCLUSION Acetaminophen is a safe and effective pharmacologic treatment to reduce the significance of the hsPDA in some infants beyond 2 weeks of age, as shown by ECHO and BNP data.

ABBREVIATIONS ALT, alanine transaminase; AST, aspartate transaminase; BNP, B-type natriuretic peptide; tx, treatment; COXI, cyclooxygenase inhibitor; ECHO, echocardiogram; FiO_2, fraction of inspired oxygen; hsPDA, hemodynamically significant PDA; IV, intravenous; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus; RCT, randomized controlled trial

KEYWORDS acetaminophen; hemodynamically significant PDA; neonate; patent ductus arteriosus

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Introduction

The ductus arteriosus is an important structure in fetal life. However, if it remains patent after birth, ductal shunting may result in severe morbidity and mortality, especially in premature infants less than 30 weeks' gestation. The morbidities associated with a patent ductus arteriosus (PDA) include pulmonary overcirculation, pulmonary edema or hemorrhage, and cardiac strain. Additionally, the shunting resulting in systemic hypoperfusion can be associated with renal failure and necrotizing enterocolitis (NEC).[1–4]

While a PDA is a common finding in premature infants, it does not always require treatment. There has been a national trend toward not treating a PDA unless there is clinical evidence of instability.[5] Signs and symptoms of a hemodynamically significant PDA (hsPDA) include hypotension, poor capillary refill, feeding intolerance, increase in oxygen requirement, and decreased urinary output[6] and may indicate the need for therapy. An echocardiogram (ECHO) is the confirmatory diagnostic test and can provide information regarding the size, direction, and degree of shunting contributing to these clinical findings.[7]

Non-selective cyclooxygenase inhibitors (COXIs)—indomethacin and ibuprofen—are considered the standard pharmacologic treatment for hsPDA. These medications block the cyclooxygenase component in the synthesis of prostaglandin, which acts to keep the ductus open after birth. The 2 medications have been well studied with an approximate 60% to 70% efficacy at closing the ductus in the first 2 weeks of age.[8] When an infant is at risk for worsening morbidity due to a hsPDA, but is older than 2 weeks of age, non-selective COXIs are thought to be less effective as postnatal age increases.[9,10]

Additionally, the non-selective medications can have undesired side effects such as renal failure,

decreased mesenteric blood flow, spontaneous intestinal perforation, and antiplatelet activity.[11,12] Some studies have noted that non-selective COXIs may negatively impact nephrogenesis, and thus, clinicians should be cautious in their use in preterm infants.[13,14] When medical management fails, surgical ligation is the definitive treatment for the closure of hsPDA. However, this intervention has been associated with an increased risk of NEC, bronchopulmonary dysplasia, and severe intraventricular hemorrhage (IVH) in addition to the immediate risks of hemodynamic instability, surgical bleeding, infection, and vocal cord paralysis.[15,16]

Due to these risks, researchers continue to investigate alternative therapeutic options for hsPDA closure.[17] One such option is acetaminophen. Although the mechanism of action is not entirely understood, it is thought to have more COX-2 inhibition selectivity by blocking the peroxidase component of prostaglandin-H2 synthase.[18] Thus, its use avoids the alterations in renal and mesenteric blood flow that are associated with COX-1 inhibition.[19] There have been many studies on the use of acetaminophen in the early treatment of hsPDA, but there are relatively few studies examining efficacy in infants after 2 weeks of age.[20–24]

This study was designed to determine if acetaminophen can be an effective treatment for hsPDA in preterm infants after 2 weeks of age, which is outside the ideal therapeutic window for ibuprofen or indomethacin use.

Materials and Methods

This is an observational study performed after a practice change in our neonatal intensive care unit (NICU) when acetaminophen became available for use for hsPDA treatment given the emerging evidence of its efficacy and safety profile. This study contains both retrospective and prospective components, investigating the efficacy and safety of acetaminophen therapy for hsPDA in preterm infants after 2 weeks of age.

Study Population. This study was carried out in the NICU at Albany Medical Center. All studied infants were treated with acetaminophen at the discretion of the medical team per hospital formulary. Echocardiograms were obtained in both patient populations as part of the unit standard management of hsPDA, and would have been obtained regardless of the study, thus the cost was not covered by the study.

All babies born between 23 0/7 and 29 6/7 weeks' gestation who met the inclusion criteria of having a hsPDA, diagnosed by ECHO and determined to need treatment with acetaminophen as decided by the attending physician (not the research team) at >14 days of age, were eligible for the study. For the prospective component, parents were approached for consent prior to their infant's first dose of treatment during the observation period, to obtain B-type natriuretic peptide (BNP) levels in addition to routine blood work. Infants were excluded from the study if found to have congenital heart disease, pulmonary hypertension, pulmonary hemorrhage, alanine transaminase (ALT) and aspartate transaminase (AST) ≥ 2X the upper limit of normal[25] (i.e., AST >300 U/L, ALT >90 U/L), suspected sepsis or meningitis, pneumonia, hydrops, or major congenital malformations prior to the study start.

BNP levels were collected, along with a comprehensive metabolic panel and fractionated bilirubin level, within 24 to 48 hours before the start of therapy. Each infant then completed a 3-day course of acetaminophen (15 mg/kg/dose every 6 hours for 3 days) as per the medical team's treatment plan. The medication was administered either intravenously (IV) or enterally, depending on whether the infant already had IV access at the time of treatment. The BNP levels were remeasured, along with the infants' other routine bloodwork, within 24 hours after the last dose. All laboratory studies were collected on the same days as the ECHOs were performed.

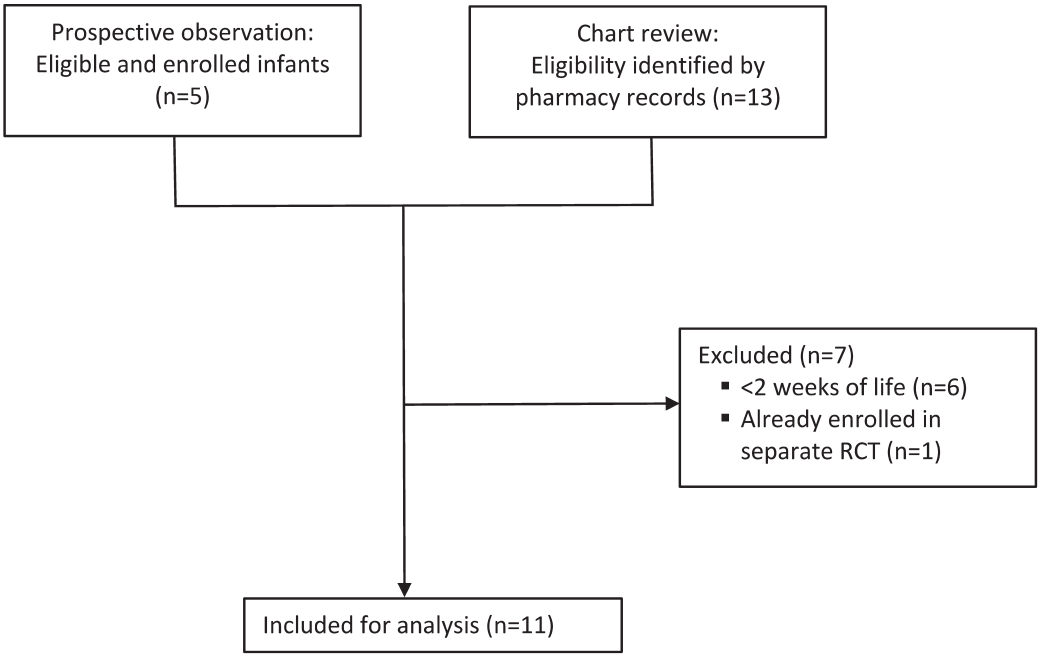
Pretreatment and posttreatment ECHOs were performed on a Philips EPIQ 7 echocardiographic scanner (Bothell, WA) by 1 of 4 board-certified pediatric cardiologists per the NICU's standard of care for a PDA undergoing pharmacologic closure. A single cardiologist (MC) reviewed all ECHOs at the end of the study, using ventricular size, left atrium to aortic root ratio, PDA diameter, and direction and pulsatility pattern of flow through the PDA to categorize the PDA into large, moderate, small, or no PDA.

Baseline characteristics of the infants were collected, including demographic data, Apgar score, exposure to prolonged rupture of membranes, antenatal steroids, maternal chorioamnionitis, or postnatally to indomethacin, ibuprofen, or acetaminophen prior to the observation period.

Outcome Measures. The primary outcome measure was PDA size change or closure based on ECHO. The secondary outcome was the change in BNP level from pretreatment to posttreatment. Other outcome measures included the change in the fraction of inspired oxygen (FiO_2) requirement, rate of NEC or spontaneous perforation, rate of significant IVH (defined as grade 3 or 4), renal or hepatic insufficiency, the requirement of a second course of pharmacologic treatment, and need for surgical ligation.

Data Analysis. GraphPad InStat version 5.04 for Windows (GraphPad Software, La Jolla, CA) was used to analyze the data. The PDA size and significance were categorized into no PDA, small, moderate, and large PDA for determining pretreatment to posttreatment changes based on the available data. The BNP level, FiO_2 requirement, and other outcome measures pretreatment and posttreatment were compared by using paired *t* test analyses. Statistical significance was set at $p \leq 0.05$.

Figure 1. Population flow diagram.



RCT, randomized controlled trial

Results

Thirteen infants were screened for eligibility for the retrospective portion, based on their receipt of acetaminophen for PDA treatment, and 5 infants were screened for the prospective component. Seven infants were eliminated from analysis as based on exclusion. All parents of infants who met eligibility criteria for the prospective component gave their consent for participation. Data on 11 infants were subsequently analyzed (Figure 1).

Demographics. The average gestational age of the infants at birth was 25.4 ± 1.8 weeks with a mean birth weight of 804 ± 285 g. Infants received late treatment with acetaminophen during the observation period at a mean gestational age of 28.5 ± 2.1 weeks and postnatal age of 23 ± 9 days. All but 1 infant received the medication intravenously. Six (54.5%) infants had received a non-selective COXI, and 2 (18.2%) had received acetaminophen prior to the study observation period (Table 1).

Primary Outcome. Ten infants had both pretreatment and posttreatment ECHOs. Four of 10 (40%) had a decrease in PDA size on ECHO (Table 2); however, this was not statistically significant (p = 0.9). No infant had complete closure immediately after the late acetaminophen course. Of the 4 infants with smaller PDAs, 3 were closed, and 1 remained open (however, was not hemodynamically significant) at time of discharge. Only 1 infant received an additional course of IV medication after the observation period.

Six infants had no change in PDA size immediately after the acetaminophen course. Of these 6 infants, the PDA of 1 infant was closed at discharge, 1 was open (but not hemodynamically significant), and 4 underwent PDA ligation. Five infants were not exposed postnatally to indomethacin or ibuprofen before acetaminophen therapy, and 3 had a decrease in PDA size (p = 0.9). Outcomes for each `patient found in Supplemental Table.

Secondary Outcomes. Five infants had complete BNP data, with 2 of 5 (40%) having a lower posttreatment level (p = 0.4) (Figure 2). Eight of 11 infants (73%; p = 0.6) had a decrease in FiO_2 requirement. (Figure 3) In the 4 infants with a smaller PDA after treatment, 3 had a decrease in FiO_2 need (p = 0.4), and 1 had a decreased BNP level (p = 0.4).

The mean arterial pressure, urine output, serum creatinine, AST, ALT, and direct bilirubin before treatment were within normal limits and had no significant changes after treatment in those infants who had complete before and after values charted (Table 3). One infant received another course of acetaminophen therapy after the observation period. Four of the 11 infants went on to have surgical ligation. All the infants who required surgical ligation had postnatal non-selective

Table 1. Baseline Characteristics of the Study Population

Characteristic	Value (N = 11)
Gestational age at birth, mean ± SD, wk	25.4 ± 1.8
Birthweight, mean ± SD, g	804 ± 285
Gestational age at first dose acetaminophen,* mean ± SD , wk	28.5 ± 2.1
Postnatal age at first dose acetaminophen,* mean ± SD, days	23 ± 9
Sex, n (%)	
Female	8 (72.7)
Male	3 (27.3)
Apgar score, mean ± SD	
1 min	4 ± 3
5 min	5 ± 2
Exposures, n (%)	
Antenatal steroids (≥1 dose prior to delivery)	7 (63.6)
Prolonged rupture of membranes	2 (18.2)
Maternal chorioamnionitis†	1 (9.1)
Postnatal indomethacin/ibuprofen‡	6 (54.5)
Postnatal acetaminophen‡	2 (18.2)

* Of observation period.
† Defined as maternal treatment.
‡ Prior to observation period.

COXI exposure prior to the observation period. No infant in this cohort developed significant IVH. One infant was diagnosed with NEC on the day of, but prior to the start of, the acetaminophen course. The medical team's decision to use acetaminophen was due to the diagnosis of NEC, feeling that a non-selective COXI was contraindicated. This infant ultimately died as a result of NEC totalis 6 days after the acetaminophen course completed. The other infant who died did so at day of life 163 due to severe BPD (Table 4).

Table 2. Primary Outcome

Patient	PDA Size	
	Pretreatment	Posttreatment
1	Moderate	Small
2	Small	Small
3	Moderate	N/A
4	Moderate	Moderate
5	Moderate	Moderate
6	Moderate	Moderate
7	Moderate	Small
8	Moderate	Moderate
9	Small	Small
10	Large	Small
11	Large	Large

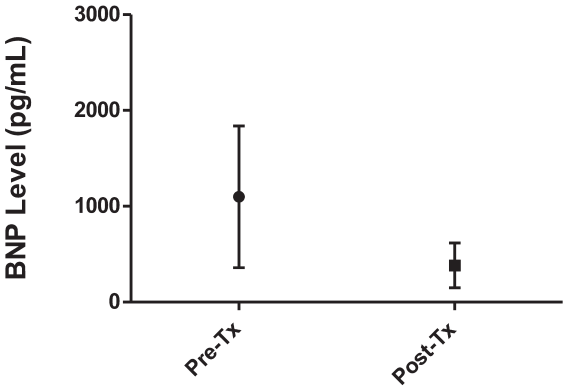
PDA, patent ductus arteriosus

Discussion

This observational study examines the use of acetaminophen as a treatment for hsPDA in preterm infants who are more than 2 weeks of age. There was a decrease in the size of the PDA after acetaminophen therapy in 40% of the infants with complete ECHO data. Additionally, there were no adverse events associated with the medication in our study population.

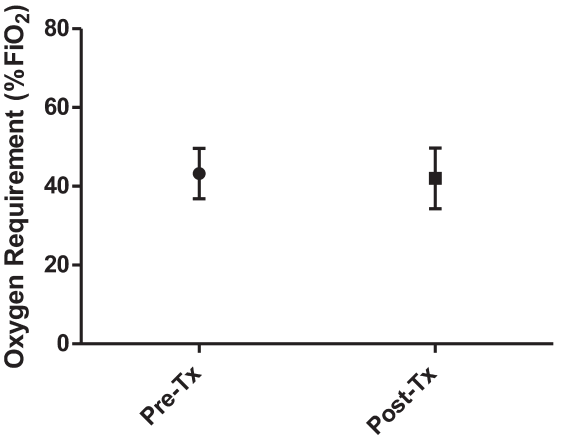
Acetaminophen is becoming more commonly used as a therapy for hsPDA. Many infants whose PDAs are left untreated will have spontaneous closure, which is why there has been a shift toward less treatment. However, the struggle of treatment options still exists for those infants who are determined to need intervention to prevent potential morbidities such as pulmonary overcirculation, cardiac strain, and systemic hypoperfusion. A recent Cochrane review, including 8 studies comparing acetaminophen efficacy and safety to that of indomethacin, ibuprofen, and placebo, concluded that acetaminophen has comparable efficacy to indomethacin and ibuprofen with fewer renal and hepatic side effects.[17] However, they did not perform any subgroup analysis on those infants >14 days of age at the start of treatment. Several retrospective reviews have investigated late acetaminophen therapy for hsPDA and found it to be effective at either closing the PDA or decreasing need for ligation.[20–24] However, there is noteworthy variability in the duration of treatment, anywhere from 3 to 7 days, which has been sug-

Figure 2. B-type natriuretic peptide (BNP) levels before and after acetaminophen treatment.



Tx, treatment
Data are given as mean ± SEM (p = 0.4).

Figure 3. Fraction of inspired oxygen (FiO_2) requirement before and after acetaminophen treatment.



Tx, treatment
Data are given as mean ± SEM (p = 0.5).

gested to impact closure rates.[26,27] Additionally, there is variation in the route of medication administration. Only 1 study, by El-Khuffash et al,[20] in addition to ours, evaluated infants after IV acetaminophen. Although we did not achieve immediate posttreatment acetaminophen closure in any infants in our cohort, several had improved hemodynamic significance deemed by the medical team not to require further pharmacologic or surgical treatment.

Based on our literature review there was only 1 study[28] that challenged the idea that non-selective COXIs are less effective beyond 2 weeks of age. Lainwala et al[28] found that PDA ligation occurred at a similar rate in their cohort, whether treated early or late with non-selective COXIs. PDA diagnosis in that study was determined by echocardiographic findings or clinical symptoms (e.g., murmur, bounding pulses, wide pulse pressure). Therefore, it seems that infants who may not have had a hsPDA were included in the 84% of very low-birth-weight infants who were treated. It is possible that more infants were medically treated than would be in the current environment of watchful waiting. This may have affected their treatment and ligation rates and have had an impact on their findings. Additionally, the authors used surgical ligation as a surrogate for failure of COXI treatment and note that their ligation rate was 14% to 15% compared with 5% to 6% reported by others, which may influence their outcomes.

A marker of cardiac strain, BNP levels have been suggested as useful in determining ductal significance in preterm infants in multiple studies[1,29–31]; however, they were all done when treatment was given within the first 2 weeks of life. To our knowledge, this is the first study using BNP levels to assess hsPDA beyond 2 weeks of life. While there was no statistically significant decrease in BNP levels in our cohort immediately after acetaminophen treatment, this may suggest the infant had longer-standing cardiac strain and therefore the BNP level may take more time to decrease after treatment when compared with an infant treated early. If we had obtained serial BNP levels until closure, as many of the hsPDAs were closed at the time of discharge, we may have seen a decrease.

As of the writing of this manuscript, there is only 1 study that mentions a possible adverse association with late acetaminophen therapy. Mashally et al[23] noted an increase in the risk of chronic lung disease in the epoch when acetaminophen was being used compared

Table 3. Secondary Outcomes

Measurement	Pretreatment, Mean ± SD	Posttreatment, Mean ± SD	p value
Mean arterial pressure, mm Hg	39.0 ± 9.1	40.2 ± 9.3	0.60
Urine output, mL/kg/hr	4.0 ± 3.9	3.9 ± 1.5	0.81
Serum creatinine, mg/dL	0.7 ± 0.3	0.7 ± 0.5	0.91
AST, IU/L	20.7 ± 8	22.7 ± 5.6	0.65
ALT, IU/L	10.6 ± 12	8.7 ± 4.6	0.58
Direct bilirubin, mg/dL	0.8 ± 0.5	0.8 ± 0.5	0.88

ALT, alanine aminotransferase; AST, aspartate aminotransferase

Table 4. Additional Outcomes of Study Population

Parameter	Value, n (%)
Received second course of treatment after observation period	
Acetaminophen, IV	1 (9.1)
Ibuprofen	0
PDA ligation	4 (36.4)
IVH ≥ grade 3	0
NEC	1 (9.1)
SIP	2 (18.2)
Death	2 (18.2)

IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; SIP, spontaneous intestinal perforation

with that in the epoch when acetaminophen was not a therapeutic option. However, the increase in risk of chronic lung disease was only for those infants in the acetaminophen epoch who neither received any treatment for the hsPDA nor had the diagnosis of a PDA, indicating that this association cannot be linked to the medication or hsPDA.

Interestingly, in a subgroup analysis of our population of infants who had never been exposed to either ibuprofen or indomethacin, 3 posttreatment hsPDAs were smaller, and none required surgical ligation. However, it is unknown whether this is a result of having a hsPDA that was more resistant to treatment or that somehow the mechanism of action of ibuprofen/indomethacin interfered with the efficacy of acetaminophen when used later. Of the 2 infants exposed to acetaminophen before hsPDA treatment, one had a smaller PDA immediately after the observation period course, and the other had no change in size. Neither received additional treatment for their PDA, nor did they require surgical ligation. Further studies are needed.

Enrollment rates for the study were estimated from routine practice in our NICU during the 2 years before the study began. Given the more recent trend in our unit and across the nation toward watchful waiting, enrollment was much slower than predicted.[5] The challenge in recruiting a sample size that would show statistical significance becomes more difficult as the number of infants who require treatment becomes smaller. If the trend continues, and fewer infants are treated at less than 2 weeks of life, finding a safe and effective medication beyond this time point is necessary for those infants who become ill enough to require treatment.

Conclusion

This study suggests that acetaminophen is a safe and effective treatment to reduce the size and clinical significance of hsPDA after 2 weeks of age when the efficacy of non-selective COXIs decreases. As current practice trends will increase the number of infants with hsPDA who are not treated early, it becomes imperative to have a pharmacologic option to treat these infants at a later time point. Larger studies are needed.

ARTICLE INFORMATION

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Ethical Approval and Informed Consent The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation. The study was approved by the hospital's Institutional Review Board. Informed consent was obtained from parents of all prospectively studied infants, with no additional costs for study labs (BNP levels) incurred by the family. Parental consent was not required for chart review portion of this study.

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