JPPT | Single Center Retrospective Study

Enteral Feedings Do Not Increase the Risk of NEC in ELBW Infants Undergoing Treatment of Patent Ductus Arteriosus With Acetaminophen

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OBJECTIVE Acetaminophen (APAP) is an alternative to indomethacin and ibuprofen for treatment of patent ductus arteriosus (PDA). The side effect profile of non-steroidal anti-inflammatory drugs (NSAIDs) presents enteral feeding safety concerns; however, the safety of enteral feeding on APAP is largely unknown. Optimal feeding strategies during pharmacological PDA treatment are unknown, leading to practice variation. This study aims to assess the incidence of adverse gastrointestinal (GI) outcomes in neonates treated with APAP for PDA closure while receiving enteral feedings.

METHODS Single-center retrospective cohort study of 59 extremely low birth weight (ELBW), premature neonates who received APAP for PDA treatment divided into Low Volume (LV; ≤ 20 mL/kg/day) and High Volume (HV; > 20 mL/kg/day) enteral feeding groups. The primary outcome was the incidence of any suspected or confirmed necrotizing enterocolitis (NEC). Timing of nutrition milestones, parenteral nutrition (PN) days, and adverse outcomes (feeding intolerance, liver dysfunction, death prior to discharge) were evaluated.

RESULTS The incidence of suspected or confirmed NEC was 19.5% in the LV group and 13.3% in the HV group (p = 0.593). The HV group reached full feeds 6 days sooner (18 vs 24 days, p = 0.024) and had fewer PN days (17 vs 23.5 days, p = 0.044) with no difference in adverse outcomes.

CONCLUSIONS Provision of > 20 mL/kg/day of enteral feeds during APAP treatment of PDA decreased time to full feeds and PN days compared to trophic feedings (≤ 20 mL/kg/day) with no difference in adverse GI outcomes. Continuing enteral feeding during APAP PDA treatment appears safe while improving achievement of nutritional milestones.

ABBREVIATIONS ALT, alanine aminotransferase; APAP, acetaminophen; AST, aspartate transaminase; ELBW, extremely low birth weight; GI, gastrointestinal; HV, high-volume; LV, low-volume; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NPO, *nil per os;* NSAID, non-steroidal anti-inflammatory drug; PDA, patent ductus arteriosus

KEYWORDS acetaminophen; extremely low birth weight; feeding strategies; necrotizing enterocolitis; patent ductus arteriosus; preterm

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Introduction

Patent ductus arteriosus (PDA) is a common congenital heart defect which accounts for 5-10% of all congenital heart disease and has an incidence as high as 20%–60% in preterm infants.[1] PDA is a source of significant morbidity and a risk factor for the development of necrotizing enterocolitis (NEC).[2,3] The presence of a hemodynamically significant PDA can cause intestinal hypoperfusion due to diastolic reversal of flow in the abdominal aorta leading to impaired mesenteric perfusion.[4] Standard drug therapies for PDA treatment include the prostaglandin inhibitors ibuprofen and indomethacin. Indomethacin has been shown to cause vasoconstriction of splanchnic arteries, further contributing to intestinal hypoperfusion.[5] In 2011, acetaminophen (APAP) was introduced in case reports as an alternate treatment modality for PDA closure when patients have contraindications to NSAIDs.[6,7] A recent Cochrane meta-analysis compared APAP vs ibuprofen, indomethacin, or placebo in 916 preterm infants with PDA.[8] Conclusions from the study showed that APAP closed PDA at higher rates than placebo and similar rates as prostaglandin inhibitors with fewer adverse effects, including

decreased risk for gastrointestinal (GI) bleeding or stools positive for occult blood.

There is limited consensus regarding the optimal feeding regimen during pharmacologic treatment for PDA closure in early life, leading to wide practice variation across Neonatal Intensive Care Units (NICUs) and even among neonatologists within the same unit.[9] The digestion of enteral feeds requires an adequate mesenteric blood supply, which can be impaired for infants with hemodynamically significant PDAs. However, delayed initiation or interruption of enteral feeds is associated with intestinal mucosal atrophy and increased risk of GI bacterial overgrowth and colonization.[4,9,10] One strategy to reduce the risk of GI injury during PDA treatment includes providing trophic feeds. Clyman et al[11] randomly assigned 177 preterm infants with birth weights ≤ 1250 grams and birth gestational ages < 30 6/7 weeks to receive trophic feeds (15 mL/kg/day) or remain nil per os (NPO) during PDA treatment with indomethacin or ibuprofen and found no difference in the incidence of NEC between these groups.[11] A retrospective cohort study from 2016 evaluated three enteral feeding strategies (no feedings, ≤ 60 mL/kg/day feedings, > 60 mL/kg/day enteral feedings) during indomethacin PDA treatment and found no differences in NEC incidence among the groups.[12]

These studies suggest that continuing enteral feedings during PDA treatment with the prostaglandin inhibitors indomethacin and ibuprofen does not meaningfully increase the risk of NEC. However, there are limited studies available evaluating the impact of enteral feeding strategies on GI outcomes when APAP is used for PDA treatment. As APAP's mechanism of action does not acutely decrease mesenteric blood flow like indomethacin, enteral feeding during PDA treatment with APAP should not meaningfully increase risk of intestinal injury.[13]

The primary goal of this study was to assess the incidence of suspected or confirmed NEC in neonates who were undergoing treatment of a PDA with APAP. We hypothesized that a High Volume (HV) enteral feeding group would achieve more nutritional milestones compared to a Low Volume (LV) feeding group without an increased incidence of NEC or other GI associated adverse events.

Methods

Study Population. This was a retrospective cohort study of a convenience sample of infants of any gestational age admitted to Rush University Medical Center's NICU from September 2015 to September 2020 who received at least one dose of APAP as treatment for PDA closure. Patients were identified for inclusion from the institution's electronic medical record. When APAP was prescribed, it was given by intravenous or enteral route and dosed as 15 mg/kg/dose every 6 hours for 12 doses per course and could be repeated for a total of 2 courses at the discretion of the medical team. Neonates were excluded if they had a diagnosis of NEC, other GI disorder, spontaneous intestinal perforation (SIP), or known major anomalies (anatomical, chromosomal, or cardiac) prior to the initiation of APAP.

Study Design. The decision to initiate pharmacologic PDA treatment and the choice of treatment agent for PDA closure was determined by the primary medical team. Enteral feeding strategies employed were based on the unit's feeding protocol at the time of PDA treatment and varied by the attending physician and medical team preference. Two main enteral feeding strategies were identified. Patients were retrospectively separated into two groups based on enteral feeding volumes during the PDA APAP treatment period: LV (feeds ≤ 20 mL/kg/day) and HV (feeds > 20 mL/kg/day).

The primary study objective was to assess the incidence of suspected (defined as Bell's Criteria Stage I) or confirmed (defined as Bell's Criteria Stage ≥II) NEC in neonates treated with APAP for PDA closure while receiving LV compared with HV enteral feeds. Patients were evaluated for NEC over the course of their entire admission, and onset of NEC was categorized into three phases: Onset during treatment, within 7 days of treatment completion, and any point > 7 days of treatment completion.

Secondary outcomes included the duration of parenteral nutrition (PN), time to reach full enteral feeds (≥ 120 mL/kg/day), incidence of feeding intolerance, duration of hospital stay, and need for PDA surgical ligation or device closure, for example, wire mesh device. Feeding intolerance was defined as the presence of ≥ 2 of the following at the same time: abdominal/gaseous distention, emesis > 3 mL, occult blood in stool, ileus, dilated bowel loops on X-ray or ultrasound, patient placed NPO, or if enteral feeds were held.

Safety outcomes included the incidence of liver dysfunction, need for early treatment discontinuation or dose reduction, and death prior to NICU discharge. Liver dysfunction was defined as conjugated bilirubin ≥ 0.9 mg/dL, aspartate aminotransferase (AST) ≥ 113 U/L, and alanine transaminase (ALT) ≥ 68 U/L.

Statistical Analysis. Sample size was determined on the basis of convenience. Descriptive statistics include counts (percentages), mean (SD), and median (25th–75th percentile) as appropriate based on distribution. The incidence of primary and secondary outcomes was evaluated using the Mann-Whitney *U* test for continuous variables and the Pearson χ^2 test for categorical variables. All statistical analyses were performed using SPSS Statistics software version 26 (IBM, Armonk, NY). Significance was set at $\alpha < 0.05$.

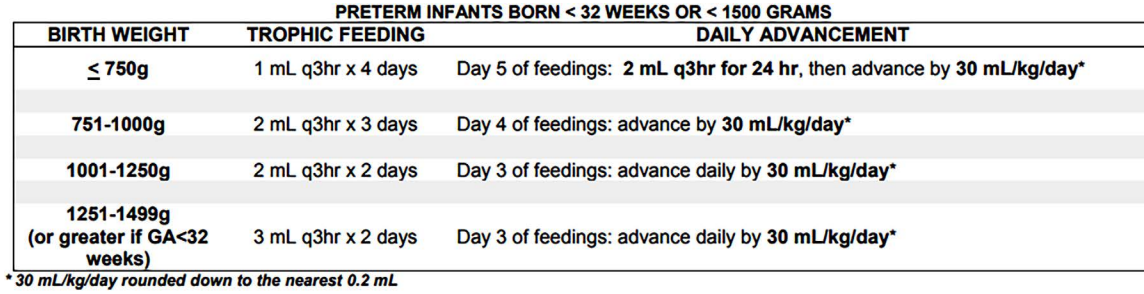
Results

A total of 56 patients were included in the final analysis (see Supplemental Figure). The LV group included 41 patients. Of these, 1 (1.8%) was made

NPO, and 40 (71.4%) received trophic enteral feeds (≤ 20 mL/kg/day) on the first day of APAP treatment. The HV group included 15 patients. Of these, 3 (5.4%) received restricted enteral feeds (21 to < 60 mL/kg/day), and 12 (21.4%) received liberalized enteral feeds (≥ 60 mL/kg/day) on the first day of APAP treatment.

Baseline characteristics (Table 1) were evenly distributed among both groups except for incidence of

Figure. 2023 Rush University Medical Center NICU feeding protocol.



PRETERM INFANTS BORN < 32 WEEKS OR < 1500 GRAMS

BIRTH WEIGHT	TROPHIC FEEDING	DAILY ADVANCEMENT
≤ 750g	1 mL q3hr x 4 days	Day 5 of feedings: **2 mL q3hr for 24 hr**, then advance by **30 mL/kg/day***
751-1000g	2 mL q3hr x 3 days	Day 4 of feedings: advance by **30 mL/kg/day***
1001-1250g	2 mL q3hr x 2 days	Day 3 of feedings: advance daily by **30 mL/kg/day***
1251-1499g (or greater if GA<32 weeks)	3 mL q3hr x 2 days	Day 3 of feedings: advance daily by **30 mL/kg/day***

30 mL/kg/day rounded down to the nearest 0.2 mL

Table 1. Baseline Characteristics

	Low-Volume N = 41	High-Volume N = 15	p value
Male sex, n (%)	22 (53.7)	8 (53.3)	0.983
Gestational age at birth (wk+days), median (25th–75th percentile)	25+0 (24+1–26+2)	25+1 (24+4–25+5)	0.810
Birth weight (kg), median (25th–75th percentile)	0.7 (0.64–0.87)	0.64 (0.55–0.88)	0.267
Race			0.571
Asian, n (%)	1 (2.4)	0 (0)	
Black or African American, n (%)	25 (61)	9 (60)	
Hispanic or Latino, n (%)	7 (17.1)	5 (33.3)	
White, n (%)	7 (17.1)	1 (6.7)	
Other race, n (%)	1 (2.4)	0	
Maternal history			
Receipt of antenatal steroids, n (%)	4 (9.8)	3 (20)	0.305
Gestational diabetes, n (%)	40 (97.6)	12 (80)	**0.024**
C-Section, n (%)	20 (48.8)	4 (26.7)	0.139
Multiparity, n (%)	36 (87.8)	12 (80)	0.460
APGAR scores			
APGAR 1, median (25th–75th percentile)	4 (2–6)	3 (2–5)	0.153
APGAR 5, median (25th–75th percentile)	5 (4–7)	6.5 (5–7)	0.877
APGAR 10, median (25th–75th percentile)	8 (7–8)	7 (6.75–8)	0.370
Surfactant, n (%)	35 (85.4)	14 (93.3)	0.425
*Resuscitation at delivery, n (%)	41 (100)	15 (100)	—
Small for gestational age			
<10%, n (%)	4 (9.8)	3 (20)	0.305
<3%, n (%)	1 (2.4)	1 (6.7)	0.450
Volume of feeds prior to APAP (mL/kg/day), median (25th–75th percentile)	10.26 (8.57–14.04)	65.45 (50.50–133.33)	**<0.001**
Volume of feeds on Day 1 of APAP (mL/kg/day), median (25th–75th percentile)	10.26 (8.69–12.55)	79 (65.45–138.72)	**<0.001**

APGAR, appearance, pulse, grimace, activity, and respiration; APAP, acetaminophen

* Resuscitation at delivery defined as requiring positive pressure ventilation or cardiopulmonary resuscitation.

Table 2. PDA Characteristics and Outcomes

	Low-Volume N = 41	High-Volume N = 15	p value
*Initial size of PDA			0.831
Small, n (%)	3 (7.3)	1 (6.7)	
Small to moderate, n (%)	1 (2.4)	0 (0)	
Moderate, n (%)	8 (19.5)	5 (33.3)	
Moderate to large, n (%)	7 (17.1)	2 (13.3)	
Large, n (%)	22 (53.7)	7 (46.7)	
Shunting before APAP, n (%)	40 (97.6)	15 (100)	0.542
Full closure of PDA after final course of APAP, n (%)	4 (9.8)	4 (2.7)	0.109
	Low-Volume n = 37	**High-Volume n = 11**	**p value**
PDA changes if APAP did not result in full closure			**0.028**
PDA size the same as prior to APAP, n (%)	16 (43.2)	1 (9.1)	
Reduction in size but PDA still present and clinically significant, n (%)	12 (32.4)	4 (36.4)	
PDA still present but no longer clinically significant, n (%)	8 (21.6)	3 (27.3)	
PDA increased in size, n (%)	1 (2.7)	3 (27.3)	

PDA, patent ductus arteriosus; APAP, acetaminophen

* Initial size of PDA as reported in echocardiogram findings.

gestational diabetes in the mother, which was higher in the LV Group. Reasons reported for initiation of APAP over indomethacin (this institution's only formulary NSAID agent) were similar between the LV and HV Groups; these included failure of indomethacin treatment (31.7% vs 46.7%, p = 0.301), presence of intraventricular hemorrhage (48.8% vs 60%, p = 0.457), thrombocytopenia (7.3% vs 6.7%, p = 0.933), renal insufficiency (31.7% vs 6.7%, p = 0.055), and other (7.3% vs 20%, p = 0.174). These other reasons included drug interactions, blood noted in residuals or secretions, and disseminated intravascular coagulation.

PDA outcomes (Table 2) showed comparable rates of a large PDA at the time of diagnosis (53.7% in the LV Group and 46.7% in the HV Group). Only four patients in each group had complete closure of their PDA after the final course of APAP. APAP was more often given by intravenous route in the LV Group (51.2% vs 13.3%) and by enteral route in the HV Group (86.6% vs 48.8%), which was a statistically significant difference between both groups (p = 0.011). Receipt of interacting medications (defined as hydrocortisone, dexamethasone, and indomethacin) prior to the initiation of APAP as well as vasoactive medication exposure (dopamine, dobutamine, and epinephrine) prior to or at the time of initiation of APAP were not significantly different between groups.

The primary outcome of any NEC (suspected or confirmed) did not differ significantly between the LV and HV Groups, with incidence of 8 of 41 patients (19.5%) in the LV Group as compared to 2 of 15 patients (13.3%) in the HV Group (p = 0.593) (Table 3). Four of 8 cases (50%) occurred > 7 days after PDA treatment in the LV Group vs 2 of 2 (100%) in the HV Group; therefore, 60% of all NEC cases occurred > 7 days after PDA treatment. NEC staging for diagnosed NEC cases did not differ significantly between the LV and HV Groups (p = 0.104); Stage 1 (suspected NEC) occurred in 7 of 8 NEC diagnoses (87.5%) in the LV Group and 1 out of 2 (50%) in the HV Group. Only 1 case of Stage III NEC occurred in this study population within the LV Group.

Infants in the HV Group achieved more nutritional milestones, including decreased duration of PN (17 [15–21] vs 23.5 [15.25–31.75] days, p = 0.044) and reduced time to reach full enteral feeds, both from time of last APAP dose (3 [0–7] vs 13 [6.25–18] days, p = <0.001) as well from time of birth (18 [15–24] vs 24 [16.25–33] days, p = 0.024). There were no differences in feeding intolerance between the 2 groups within 72 hours prior to the initiation of APAP (p = 0.933), during APAP treatment (p = 0.702), within 72 hours after the final dose of the final course of APAP was given (p = 0.275), and from 72 hours through 7 days after the final dose of the final course of APAP was given (p = 0.876). Adverse effect outcomes (Table 3) were similar between the LV and HV Groups, including need for early discontinuation of APAP (p = 0.792), need for APAP dose reduction (p = 0.542), and occurrence of liver dysfunction (Table 3). Death prior to NICU discharge was not statistically significantly different between the 2 groups: 6 of 41 patients (14.6%) in the LV Group as compared with 1 of 15 patients (6.7%) in the HV Group (p = 0.542).

Discussion

In this study, we found that the provision of liberalized HV enteral feedings during PDA treatment with APAP

Table 3. Outcomes

	Low-Volume N = 41	High-Volume N = 15	p value
NEC (suspected or confirmed), n (%)	8 (19.5)	2 (13.3)	0.593
*NEC Stage			0.104
Stage I, n (%)	7 (87.5)	1 (50)	
Stage II, n (%)	0 (0)	1 (50)	
Stage III, n (%)	1 (12.5)	0 (0)	
Stage IV, n (%)	0 (0)	0 (0)	
NEC timing			0.435
During treatment, n (%)	2 (25)	0 (0)	
Within 7 days of treatment, n (%)	2 (25)	0 (0)	
>7 days after treatment, n (%)	4 (50)	2 (100)	
Surgical NEC, n (%)	1 (12.5)	0 (0)	0.598
Length of stay (days), median (25th–75th percentile)	124 (97–159)	123 (107–154)	0.912
∞Need for PDA surgical ligation or device closure after APAP, n (%)	14 (35)	2 (13.3)	0.115
Duration of parenteral nutrition (days), median (25th–75th percentile)	23.5 (15.25–31.75)	17 (15–21)	**0.044**
Time to reach full enteral feeds from last APAP dose (days), median (25th–75th percentile)	13 (6.25–18)	3 (0–7)	**<0.001**
Time to reach full enteral feeds from date of birth (days), median (25th–75th percentile)	24 (16.25–33)	18 (15–24)	**0.024**
Feeding intolerance			
€Pre-APAP administration, n (%)	3 (7.3)	1 (6.7)	0.933
±During APAP, n (%)	4 (9.8)	2 (13.3)	0.702
Λ72h post-APAP administration, n (%)	3 (7.3)	0 (0)	0.275
ʍ7 days post-APAP administration, n (%)	6 (14.6)	2 (13.3)	0.876
Need for early discontinuation of APAP, n (%)	2 (4.9)	1 (6.7)	0.792
Need for dose decrease, n (%)	1 (2.4)	0 (0)	0.542
Liver function: conjugated bilirubin (mg/dL)			
Most recent conjugated bilirubin prior to initiation of APAP, median (25th–75th percentile)	0.53 (0.41–0.64)	0.40 (0.35–0.48)	0.064
Post-treatment conjugated bilirubin, median (25th–75th percentile)	0.69 (0.63–0.95)	0.65 (0.47–0.79)	0.14
†Bilirubin Abnormality, n (%)	10 (24.4)	1 (6.7)	0.139
Liver function: AST/ALT (U/L)	39 (25–58)	33 (27–43)	0.227
Most recent AST prior to initiation of APAP, median (25th–75th percentile)	33 (27–43)	26 (22–37)	0.176
Post-treatment AST, median (25th–75th percentile)	6 (6-10)	6 (6-8)	0.839
Most recent ALT prior to initiation of APAP, median (25th–75th percentile)	7 (6-12)	6 (6-7)	0.187
Post-treatment ALT, median (25th–75th percentile)	1 (2.4)	0 (0)	0.542
‡AST/ALT abnormality, n (%)			
Death prior to NICU discharge, n (%)	6 (14.6)	1 (6.7)	0.452

NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; APAP, acetaminophen; AST, aspartate aminotransferase; ALT, alanine transaminase

* NEC stages as defined in the methods section.
∞ Low-volume group: n = 40; High-volume group: n = 15
€ 72 h prior to first dose
± During course(s) of APAP treatment
Λ Within 72 h after last dose of the last course of APAP
ʍ 72 h to 7 days after the last dose of the last course of APAP
† Bilirubin abnormality: Conjugated Bili 1.5× the upper limit of normal (ULN); Normal C. Bili: < 0.6 (Abnormal 0.9).
‡ AST/ALT abnormality: AST or ALT >1.5× ULN; Normal AST: 25–75 U/L (Abnormal 113 U/L); Normal ALT: 13–45 U/L (Abnormal 68 U/L).

improved nutritional milestones including reduced time from birth to full enteral feedings, reduced time from completion of PDA treatment to full enteral feedings, and reduced PN duration. No increase in GI associated adverse outcomes were found in the HV Group including: any stage of NEC, feeding intolerance, liver toxicity, or death before NICU discharge. There was only 1 case of NEC Stage II or greater in each feeding group. The only case of Stage III or higher confirmed NEC within the study population occurred in the LV Group (receiving < 20 mL/kg/day of enteral feedings).

Although previous studies have evaluated enteral feeding safety during NSAID treatment for PDA, there is currently very little published literature evaluating enteral feeding safety during APAP treatment. Published studies evaluating APAP efficacy for PDA closure provide few details in their methods regarding enteral feeding regimens during pharmacologic treatment.[11,12] In a randomized control trial, Clyman et al[11] found continuing trophic feedings during PDA treatment with ibuprofen or indomethacin decreased time to reach full enteral feeds (13.1 days vs 10.3 days, $p < 0.05$).[11] In this study, neonates were randomly assigned to receive either trophic enteral feeds (Feeding Group) or no enteral feeds (Fasting Group) during PDA treatment with either indomethacin or ibuprofen. Their study did not comment on feeding safety during APAP treatment. In our study, we found that neonates provided LV enteral feeds (NPO or trophic feedings of ≤ 20 mL/kg/day) achieved full feeds of 120 mL/kg/day at a median of 13 days, while neonates provided HV feedings (> 20 mL/kg) during PDA treatment reached full feeds faster than the neonates who were provided trophic feeds (3 days vs 13 days). The neonates included in the Clyman et al[11] study were comparable in age and weight to our study cohort (mean birth GA 26 weeks vs birth GA 25 weeks in our cohort). The Clyman et al[11] study included infants with a birth weight up to 1.25 kg. Although our study's inclusion criteria was not based on weight, all neonates included in our study were < 1 kg at birth. The Clyman et al[11] study offers evidence to support the safety of trophic feedings during PDA treatment with indomethacin and ibuprofen. Our study additionally supports the safety of feedings during PDA treatment while providing evidence for the safety of a liberalized enteral feeding approach during PDA treatment with APAP to achieve improved nutritional milestones without increased adverse events. Although achievement of nutritional milestones occurred earlier for the infants in the HV Group, there was no difference in length of stay between the LV and HV Groups in our study.

In this study, we compared the incidence of NEC during APAP treatment for PDA closure between 2 distinct enteral feeding strategies. Although standard rates of PDA closure in our center's NICU are unknown, the rates of NEC have historically been low. According to Vermont Oxford Network data from 2011–2019, rates of NEC at our center ranged between 1.6% and 5.8%, compared with the rate of 7% reported from similar hospital systems in both the United States and Canada during the same time period.[14] Due to this baseline low rate of NEC, a combination of suspected and confirmed NEC was used to define the primary outcome of our study to evaluate for feeding safety and GI intolerance. Rates of confirmed NEC (Bell's Stage II or above) in our study were 2% in the LV group and 6% in the HV group, consistent with reported ranges. Previous studies have shown that the presence of a PDA itself is an independent risk factor for NEC and that treatment with NSAIDs does not lead to an increased NEC risk.[3,12] While our study did not find a difference in rates of NEC between LV and HV feeding groups, it adds to the body of literature which supports the safety of enteral feeding provision during the medical treatment of PDA, specifically with APAP.

This study has several limitations. Most importantly, it is a retrospective review in a single center with a relatively small sample size. The first case of APAP use for PDA treatment in our NICU occurred in 2015. While this study reflects the majority of APAP treatment courses in our NICU, our sample size of 56 infants is substantially smaller than a similar study performed by Louis et al[12] who evaluated the incidence of NEC utilizing 3 feeding strategies during PDA treatment with indomethacin in 415 premature neonates. While the authors pointed out that their study was possibly underpowered to detect a difference in rates of NEC, from our current review of the literature, theirs is the largest study currently published addressing this topic. Louis et al[12] were able to evaluate a primary outcome of NEC ≥ Stage II. Due to our study's small sample size, our primary outcome included a combination of both suspected and confirmed NEC as the primary outcome in order to evaluate for feeding intolerance and GI distress. Our study is underpowered to detect differences in rates of confirmed NEC. Understanding this, we believe our combined outcome of suspected and confirmed NEC is a stronger marker for adverse feeding outcomes related to pharmacologic PDA treatment than nonspecific feeding intolerance.

Our study may suffer from potential selection bias between the LV and HV Groups as patients with a history of feeding intolerance may have started in the LV Group. Differences between feeding volumes existed in the groups prior to APAP therapy and may have been due to a variety of factors; therefore, differences observed may not correlate to APAP therapy. Feeding intolerance was measured only up to 72 hours prior to the initiation of APAP, so we may not have uniformly captured this difference. We also did not measure growth over time to better understand the effects of our interventions on patients' overall growth. Although birth weight was collected as a baseline characteristic, patients' weight or other growth measures were not

re-evaluated throughout the study or at discharge. While not an objective of this study, we recognize the value this type of outcome could provide to clinical decision-making.

Additionally, our study is limited based on our institutional practices and preferences. Our institution utilizes a three-day treatment course of APAP. It is unknown whether the incidence of NEC or other GI outcomes reported in our study would change should an institution choose to use a longer APAP course for treatment. We also saw that it was our institution's preference to utilize two routes of administration for APAP. It is unclear whether institutions who prefer one route over another would find different outcomes from our study.

A final limitation of our study is known variation in feeding practices during the 5-year study period. While the current feeding protocol used on our unit for preterm infants born <32 weeks or <1500 grams can be reviewed in the Figure, there were slight changes to enteral feeding protocols for extremely low birth weight infants in our NICU throughout this 5-year review that led to the establishment of our current protocol (see Figure) Feeding strategies were also affected by each patient's attending physician and the preferences of the primary medical team. It is likely that there was variability in the way enteral feeds were provided and advanced amongst the neonates in this study. While this is a potential interpatient confounder, slight interprovider variation in feeding practices during PDA treatment may increase the external validity of our study. Prior to this study, there was limited data available in the literature regarding safety of enteral feeding during pharmacologic PDA treatment with APAP. Although our sample size is relatively small, this preliminary study showed that infants receiving higher volume enteral feedings during APAP PDA treatment showed improved achievement of nutritional milestones without any increase in adverse events as compared with infants receiving trophic feedings. Therefore, we believe it is not necessary to reduce current enteral feeding volumes when initiating APAP treatment for PDA closure in preterm infants. These preliminary findings are provocative and support randomized trials examining liberalized feedings as compared with trophic feedings in PDA treatment with APAP.

Conclusion

The provision of any volume of enteral feeds but specifically HV enteral feeds (≥ 60 mL/kg/day) during treatment of a PDA with APAP does not appear to be associated with an increased incidence of suspected or confirmed NEC. The delivery of HV enteral feeds allows for quicker achievement of full enteral feeds following APAP treatment and appears to be safe and not associated with an increased incidence of other adverse GI outcomes including feeding intolerance. Future studies with a larger sample size as well as comparative studies of GI outcomes in patients who received indomethacin or ibuprofen versus APAP for PDA closure and an assessment of various enteral feeding regimens during medicinal treatment for PDA closure will be necessary to provide more expanded evidence.

Article Information

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