Title
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Journal
The Journal of Pediatrics, 163(2)

ISSN
0022-3476

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Publication Date
2013-08-01

DOI
10.1016/j.jpeds.2013.01.057

Peer reviewed

Published in final edited form as:
J Pediatr. 2013 August ; 163(2): 406–411.e4. doi:10.1016/j.jpeds.2013.01.057.

Enteral feeding during indomethacin and ibuprofen treatment of a patent ductus arteriosus

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Abstract

Objective—To test the hypothesis that infants who are just being introduced to enteral feedings will advance to full enteral nutrition at a faster rate if they receive "trophic" (15 ml/kg/day) enteral feedings while receiving indomethacin or ibuprofen treatment for patent ductus arteriosus (PDA).

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The authors declare no conflicts of interest.

Registered with ClinicalTrials.gov: NCT00728117.

Study design—Infants were eligible for the study if they were $23^{1/7}$ – $30^{6/7}$ weeks gestation, weighed 401–1250 g at birth, received maximum enteral volumes ≤60 ml/kg/day and were about to be treated with indomethacin or ibuprofen. A standardized "feeding advance regimen" and guidelines for managing feeding intolerance were followed at each site (n=13).

Results—Infants (n=177; 26.3±1.9 wks (±SD) gestation) were randomized at 6.5±3.9 days to receive "trophic" feeds ("feeding" group, n=81: indomethacin=80%, ibuprofen=20%) or no feeds ("fasting (*npo*)" group, n=96: indomethacin=75%, ibuprofen=25%) during the drug administration period. Maximum daily enteral volumes prior to study entry were 14±15 ml/kg/day. After drug treatment, infants randomized to the "feeding" arm required fewer days to reach the study's feeding volume endpoint (120 ml/kg/day). Although the enteral feeding endpoint was reached at an earlier postnatal age, the age at which central venous lines were removed did not differ between the two groups. There were no differences between the two groups in the incidence of infection, necrotizing enterocolitis, spontaneous intestinal perforation or other neonatal morbidities.

Conclusion—Infants required less time to reach the feeding volume endpoint if they were given "trophic" enteral feedings when they received indomethacin or ibuprofen treatments.

Keywords

necrotizing enterocolitis; ductus arteriosus; indomethacin; ibuprofen; feeding intolerence; newborn

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The prostaglandin synthase inhibitors, indomethacin and ibuprofen, are the only drugs licensed in the United States for the treatment of patent ductus arteriosus (PDA) in preterm infants. Unfortunately, both drugs have gastrointestinal side effects: indomethacin decreases intestinal blood flow, inhibits the normal post prandial hyperemic response (1) and interferes with gastrointestinal mucosal barrier function (2–6). Although ibuprofen does not appear to have the same effect as indomethacin on intestinal blood flow (7, 8), it does produce similar alterations in gastrointestinal permeability (9, 10). Thus, there is a concern that the introduction of enteral feedings (which promote intestinal bacterial colonization and increase intestinal oxygen demands) may be hazardous when these drugs are used.

Because of this concern, infants enrolled in clinical trials, conducted to license indomethacin and ibuprofen for PDA treatment with the US Food and Drug Administration, were fasted (*nil per os* or *npo*) and received only intravenous nutrition during study drug administration. Currently, 85% of American neonatologists report they withhold enteral feedings when treating infants with indomethacin or ibuprofen (11).

The practice of withholding feedings and making infants *npo* may have its own unintended consequences. Studies in animals and humans demonstrate that withholding enteral nutrition and providing only parenteral nutrition for periods as short as 72 hours can cause duodenal mucosal atrophy, impaired intestinal function, abnormal gut permeability (12–17), subsequent feeding intolerance (18) and longer hospital stays (19). The longer it takes to attain full enteral nutrition, the longer infants need intravenous nutrition and the more likely they are to develop septicemia and cholestasis. Therefore, withholding feedings for several days during treatment with indomethacin or ibuprofen may be detrimental to the infant and lead to subsequent feeding intolerance.

Currently, there are no published controlled, randomized trials addressing whether it is better to feed or fast an infant during indomethacin or ibuprofen treatment. Several studies have shown that small amounts of enteral nutrition have trophic effects that can minimize some of the intestinal problems caused by total parenteral nutrition (16, 20). We hypothesized that infants who are to be treated with indomethacin or ibuprofen and who are

just being introduced to enteral feedings will advance to full enteral nutrition at a faster rate if they receive "trophic" enteral feedings while receiving the drug treatment. We conducted a randomized, controlled trial to test this hypothesis.

Methods

This prospective randomized study was conducted between October 2008 and June 2012 at 13 sites after obtaining Institutional Review Board approval. Written informed parental consent was obtained before enrollment. Infants were eligible for the study if they were 1) delivered between $23^{1/7}$ – $30^{6/7}$ weeks gestation, 2) weighed 401–1250 g at birth, 3) were just beginning enteral feedings (receiving ≤60cc/kg/day), and 4) were about to receive pharmacologic treatment to close their PDA. The decision to treat the PDA was made by the infants' clinical care teams. Infants were excluded from the trial if they had previously received enteral feedings volumes greater than 60 ml/kg/day or if there were contraindications for the use of indomethacin or ibuprofen, contraindications for feedings, chromosomal anomalies, congenital or acquired gastrointestinal anomalies, prior episodes of necrotizing enterocolitis or intestinal perforation, or inotropic support for hypotension at the time of entry. The presence of an umbilical artery or vein catheter was not a reason for exclusion.

Our intention was to examine the effects of the feeding intervention on the entire population of indomethacin and ibuprofen treated infants as well as on the infants in each individual drug treatment subgroup. In order to distribute the drug treatment equally among the study populations, each study site's research pharmacist initially randomized the infants to either indomethacin or ibuprofen. Following the drug treatment assignment, infants were randomized to the study's feeding intervention: either "feeding" or "fasting (*npo*)" during the "study drug administration period" (see below for definition). Block randomization at each site was stratified by birth weight (401–700 g, 701–1000 g, and 1001–1250 g) and by center.

The drug assignment was masked from the clinical staff in the beginning of the trial; however, this could not be achieved as the study progressed due to drug availability that forced both the indomethacin and the ibuprofen arms of the study to be closed at different points in time. As a result, 58% of the infants were treated with either open-label indomethacin or ibuprofen. Throughout the trial, infants received only the drug they were initially assigned if they required re-treatment of their PDA. When indomethacin was the study drug, infants received 4 doses per treatment course (0.2, 0.1, 0.1, and 0.1 mg/kg/dose at 0, 12, 24 and 48 hr, respectively, if they were ≤1000 gm at birth *and* < 7 days old, or 0.2 mg/kg/dose for each of the 4 doses if they were >1000 gm at birth *or* ≥ 7 days old). When ibuprofen was the study drug, infants received the same 3 doses of ibuprofen (independent of birthweight or postnatal age): 10, 5 and 5 mg/kg/dose at 0, 24 and 48 hr, respectively.

All infants had an echocardiogram and Doppler study performed prior to study entry to document the presence of a PDA. An echocardiogram and Doppler study were performed within 24 hours of the last dose of study drug to determine residual ductus patency. Additional courses of study drug could be administered at the discretion of the attending neonatologists who also decided if and when the PDA needed to be ligated.

Feeding Regimen

The only clinical management controlled by the study was the feeding regimen. Because the time to achieve a specific enteral feeding volume (120 ml/kg/day) was the primary endpoint of the trial, the feeding regimen needed to be directive rather than left to the discretion of the clinicians. Therefore, a standardized "feeding advance regimen" was instituted at each of the

participating centers prior to the start of the trial. The "feeding advance regimen" specified the number of days (based on birthweight) of "trophic" feedings (15 ml/kg/day) that infants had to tolerate before their enteral volumes could be increased (Table I). Criteria defining feeding intolerance and its management were also established (Table II; available at www.jpeds.com). Breast milk was the primary source of enteral nutrition. A 20 cal/oz premature formula could be substituted for breast milk if mother's milk was unavailable. Caloric fortification of enteral feedings did not occur until after the infants were tolerating the designated primary volume endpoint for the study (enteral feedings = 120 ml/kg/day).

Study intervention

Although the feeding intervention was randomized, we could not mask which intervention ("feeding" or "fasting (*npo*)") the infants received during the "study drug administration period"—the time between the first dose of study drug and 24 hours after the last dose of study drug. Infants randomized to the "feeding" group received "trophic" enteral nutrition (15 ml/kg/day) during the "study drug administration period". Infants, who received additional courses of study drug both as part of their initial PDA treatment, or later in the hospitalization, received 15 ml/kg/day of enteral nutrition during the "study drug administration period" of each additional course. Infants randomized to the "fasting (*npo*)" group were made *npo* during the "study drug administration period" of the first and any subsequent treatment courses. Once the "study drug administration period" was completed enteral feeding was returned to the volume and rates of advancement specified by the infant's standardized feeding advance regimen.

Primary endpoint and outcomes

The primary endpoint of the study was achieved when a daily enteral feeding of 120 ml/kg/day was reached. Because the postnatal age when the primary endpoint was achieved could vary, based on the age when feedings initially were started and the infants' birthweight-specific, feeding advance regimen, we created a new variable ("ideal number" of days to reach 120 ml/kg/day) to reflect the number of days an infant would be expected to take, from the day the "study drug administration period" was completed until the enteral feeding goal of 120 ml/kg/day was reached (assuming nothing interrupted the prescribed feeding advance regimen).

The "ideal number" of days to reach 120 ml/kg/day was calculated at the time of study entry, prior to randomization, and was based on the assumption that the infant would be fasted (*npo*) during the "study drug administration period". The "ideal number" of days was defined as the difference between the *Day of Feeding* at which the infant started upon completion of the "study drug administration period" (Table I), and the *Day of Feeding* on the "feeding advance regimen" when 120 ml/kg/day was anticipated to be reached. The maximum enteral volume an infant received prior to study entry determined the infant's starting position on the "feeding advance regimen" once the "study drug administration period" was completed (Table I). For example, a 600 gm birthweight infant who had never been fed, ideally should have required 11 days to reach 120 ml/kg/day (Table I). If the infant had started enteral feeding and tolerated only 1 day of 15 ml/kg/day prior to study entry, he/she would be expected to start at "*day 2*" of the standardized "feeding advance regimen" once the "study drug administration period" was completed, and "ideally" require 10 days to reach and tolerate 120 ml/kg/day (assuming no feeding difficulties occurred during the feeding advance).

The ***primary outcome*** for our study was the difference between the actual number of days required for each infant to reach 120 ml/kg/day (from the day the "study drug administration period" was completed) and the *"ideal number"* of days to reach 120 ml/kg/day. It should be

noted that the lowest difference between the actual and *"ideal number"* of days that infants randomized to the "fasting (*npo*)" group could achieve was 0 (when actual = "ideal number"); in contrast, infants randomized to the "feeding" group could have negative differences as some of the days of trophic feedings received during the "study drug administration period" could be applied to their "feeding advance regimen". For example, if the 600 gm infant, referred to above (who tolerated 1 day of 15 ml/kg/day feedings prior to study entry) was assigned to the "feeding" group, and the infant tolerated all 3 days of the "trophic" (15 ml/kg/day) feedings during the "study drug administration period" he/she could start at "*day 5*" of the standardized "feeding advance regimen" once the "study drug administration period" was completed because he/she already received 4 days of 15 ml/kg/day. If no feeding difficulties occurred, this infant could take only 7 days to reach 120 ml/kg/day and the *difference between* actual number (7 days) and *"ideal number"* (10 days, see above) to reach 120 ml/kg/day would be minus 3 (−3) days.

Sample Size

Sample size was determined using the time to reach the primary feeding volume endpoint (120 ml/kg/day). Our prior data indicated that infants with birthweights ≤1000 gm who had a PDA requiring drug treatment, achieved enteral feedings of 120 ml/kg/day at 30±13 days after birth. We estimated that we would need a total of 400 infants to detect a significant difference (of 4 days) between the "feeding" and "fasting" groups (with a probability of 80 percent) if the standard deviation was ±13 days. An interim analysis was planned, once 50% of the subjects had been enrolled, to calculate the actual standard deviation in our study population and to determine the final number of subjects to be enrolled.

We planned to complete the study in 3 years. However, several factors prevented us from completing the study during this interval: (1) indomethacin and ibuprofen became unavailable at different points in time; and (2) a significant shift in the approach to PDA treatment made many infants no longer eligible for the study (there was a shift at most sites from treating infants within the first days after delivery to treating infants later in the neonatal course, by which time many had already received enteral feedings >60 ml/kg/day). Therefore, after 3.5 years (having enrolled only 45% of the planned enrollment), we performed an early interim analysis to determine the actual number of patients needed for study enrollment. We found that the mean age (and standard deviation) at which our study population was achieving enteral feedings of 120 ml/kg/day was 22.9±9.2 days. Based on the standard deviation of ±9.2 days, we realized that we had already enrolled a sufficient number of patients to detect a significant difference of 4 days between the "feeding" and "fasting" groups (with a probability of 80 percent). Therefore, we terminated study enrollment.

Statistical Analyses

Univariate analyses were performed using the χ^2 test for categorical variables and Student t-test for continuous variables. Although this was a randomized controlled trial, some of the demographic variables were unequally distributed between the feeding and non-feeding groups (Tables III and IV; Table IV available at www.jpeds.com). Therefore, multivariable analyses were performed to adjust the study outcomes for any possible demographic differences. Demographic variables were included in the statistical models if their univariate p-value was <0.10. In addition, because 32% of the infants enrolled in the trial were twins or triplets (Table III) and 46% of the multiple gestation infants had a sibling enrolled in the trial, we used generalized estimating equations (GEE) to adjust for any non-independence of the clustered data that might be affected by shared genetic or environmental factors. Adjusted odds ratios (OR) (for binary outcomes) and correlation coefficients (for continuous outcomes) with 95% confidence intervals (CI) were calculated using GEE. When models

were unable to run using an exchangeable correlation structure, an independent correlation structure was substituted. A p-value of <0.05 was considered significant. All analyses were performed using STATA 11 (College Station, TX) statistical software.

Results

Between October 2008 and June 2012, there were 251 infants who were eligible for the study. Seventy-four were excluded because of parental refusal and 177 subjects were enrolled in the study. Because of drug shortages, only 40 infants were treated with ibuprofen, and 137 were treated with indomethacin. There were no significant demographic differences between the "feeding" and "fasting (*npo*)" arms in the total study population except for the following variables: incidence of multiple gestation births, presence of umbilical venous catheter at the time of enrollment, and age when the first enteral feeding was attempted (Table III).

Infants randomized to the "feeding" arm required fewer days to reach 120 ml/kg/day enteral feedings after the "study drug administration period" was completed (p=0.01). They also reached the study's feeding volume endpoint at a younger postnatal age (p=0.08) (Tables V and VI; Table VI available at www.jpeds.com). There were no differences between the two groups during either the feeding advance or the entire hospitalization in the incidence of infection, necrotizing enterocolitis, or spontaneous intestinal perforation (Table V).

Several demographic variables appeared to be unequally distributed between the "feeding" and "fasting (*npo*)" groups (Table III). Therefore, we performed multivariable analyses to adjust the study outcomes for any possible demographic differences. In the multivariable statistical models, we included all of the demographic variables that differed between the two groups with a p-value ≤0.10. These included: *multiple birth, RDS, Caucasian, umbilical venous catheter present at enrollment, PDA ligation during the hospitalization*, and *age when first fed* (Tables III and VII). When our analyses were adjusted for these possible demographic variations, the difference in feeding outcomes between the two study groups became even more significant: infants randomized to the "feeding" arm required fewer days to reach 120 ml/kg/day enteral feedings following the "study drug administration period" (p=0.001), and reached the study's feeding volume endpoint at a younger postnatal age (p=0.009) (Table VII).

The significant differences between the "feeding" and "fasting (*npo*)" groups were also found when the largest drug subgroup (indomethacin) was examined by itself in a multivariable *post hoc* analysis. The difference between "feeding" and "fasting (*npo*)" groups in the Indomethacin subgroup were: age when taking 120 ml/k/d = −4.17 days (−6.98 to −1.36, p=0.004), number of days to reach 120 ml/k/d after completing the "study drug administration period" = −3.61 days (−5.87 to −1.35, p=0.002), and difference between Actual and Ideal number of days to reach 120 ml/k/d = −3.62 days (−5.80 to −1.44, p=0.001).

Several other neonatal morbidities were examined in the study population. Although there appeared to be significant differences between the "feeding" and "fasting (*npo*)" groups in the incidence of BPD, Death or BPD, and Death, NEC or BPD in the univariate analysis, these differences were no longer present when the analyses were adjusted for the demographic differences between the two groups as described above (Tables V and VII).

Discussion

We found that infants who were in the beginning stages of enteral feeding required 3–4 fewer days to reach 120 ml/kg/day enteral feedings if they were given small "trophic"

feedings during the time they received indomethacin or ibuprofen. Although we observed no increase in the incidence of feeding-related morbidities, our study was only powered to detect a 1.6-fold increase in the incidence of infection and a 2.4-fold increase in necrotizing enterocolitis. Smaller increases in morbidity could have been missed; however, neither the odds ratio for infection (OR = 0.63) nor the odds ratio for necrotizing enterocolitis (NEC during the hospitalization: OR = 0.97), suggest a trend towards increased morbidity in the "feeding" group (Table VII). Our findings are similar to a recent case-controlled study that suggested that feeding infants during indomethacin treatment appears to have no detrimental effects and may decrease the time needed for infants to achieve full enteral feedings (21).

We wanted to determine if "trophic" feedings during the "study drug administration period" decreased the time to reach 120 ml/kg/day by decreasing the number of infants who developed episodes of feeding intolerance during the feeding advance. Although this was a randomized controlled trial, we could not blind the "feeding" intervention. In order to minimize any bias in determining when episodes of feeding intolerance might occur, we developed a standardized feeding advance regimen and a feeding intolerance guideline (Tables I and II) that were adhered to by all of the centers. Decisions about feeding intolerance were left to the primary care team, rather than to the study doctors. Although it appeared as if fewer infants in the "feeding" arm had their daily feeding advance delayed due to feeding intolerance or NEC, this finding did not achieve statistical significance when the analysis was adjusted for demographic differences between the treatment groups (Tables V and VII). In addition, although 33% of the total population had their feeding advance delayed by episodes of feeding intolerance, a greater number of infants had their feedings interrupted by causes unrelated to feeding intolerance (Table V): 51% of the delays were due to one or more of these "other" causes: a) PDA ligation (16%), b) sepsis workup, recurrent apneas, respiratory deterioration (32%), c) hypotension requiring inotropes (6%), or d) blood transfusions (22%). Therefore, it is unlikely that a difference in the incidence of feeding intolerance was responsible for the "feeding" group's more rapid advance to the 120 ml/kg/day endpoint. The shorter time for the infants in the "feeding" group to reach the study endpoint was due to the trophic feedings, received during the "study drug administration period", that were credited towards the required number of "trophic" feeding days mandated by the "feeding advance regimen" (Table I).

Although infants in the "feeding" arm reached the enteral feeding endpoint and stopped total parenteral nutrition at a significantly earlier age, there was no significant decrease in the age when their central intravenous line was removed. Factors other than nutrition also contribute to the need for central venous access and probably account for the wide variability in the duration of central line access and the absence of a significant effect (Table VII).

We conclude that infants, who are just starting enteral feedings, will advance to full enteral nutrition at an earlier age if they receive "trophic" enteral feedings while receiving drug treatment for a PDA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by Gerber Foundation, NIH/NCRR-CTSI (UL1 RR024131 and UL1TR000445), and a gift from the Jamie and Bobby Gates Foundation.

Abbreviations

ROP	Retinopathy of prematurity
PDA	Patent ductus arteriosus
BPD	Bronchopulmonary dysplasia
NEC	Necrotizing enterocolitis
RSS	Respiratory severity score
npo	nil per os
GEE	generalized estimating equations
DAFFII Trial	Ductus arteriosus feed or fast with indomethacin or ibuprofen Trial

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Table 1

Feeding Advance Regimen

(A) Day of Feeding	(B) Birth Weight: 401 – 700 gm ml/kg/day	(C) Birth Weight: 701 – 1000 gm ml/kg/day	(D) Birth Weight: 1001 – 1250 gm ml/kg/day
1	"*trophic*" = 15	"*trophic*" = 15	"*trophic*" = 15
2	"*trophic*" = 15	"*trophic*" = 15	"*trophic*" = 15
3	"*trophic*" = 15	"*trophic*" = 15	30
4	"*trophic*" = 15	30	45
5	"*trophic*" = 15	45	60
6	30	60	80
7	45	80	100
8	60	100	120#
9	80	120#	
10	100		
11	120#		

Primary feeding endpoint is achieved on the day baby takes 120 ml/kg/d.

Table 3

Demographics of Total Populations: univariate analyses

Demographic and Risk variables:	**Total Population**	
	Fasting (*npo*) n=96	**Feeding n=81**
Study drug-indomethacin, %	75	80
Multiple birth, %	41	21 [a]
Rupture of membranes >18h, %	18	23
Preterm labor, %	68	75
Maternal Diabetes, %	9	6
Chorioamnionitis, %	14	11
Preeclampsia, %	21	19
Betamethasone (>6hr), %	74	68
Betamethasone (>24hr), %	57	54
Antenatal antibiotics, %	50	55
Birthweight-gm, mean (SD)	873 (205)	857 (171)
Birthweight categories:		
≤700 gm, %	24	20
701–1000 gm, %	45	59
1001–1250 gm, %	31	21
Gestation-wk, mean (SD)	26.3 (2.0)	26.2 (1.8)
SGA, %	9	4
5 min Apgar <4, %	8	12
Gender-male, %	42	51
Caucasian, %	60	47 [b]
RDS, %	85	94 [b]
Surfactant, %	85	84
RSS at 24 hours-unit, mean (SD)	1.9 (1.1)	2.0 (1.6)
Vasopressors needed prior to enrollment, %	6	6
Prophylactic Indomethacin prior to enrollment, %	20	23
Hydrocortisone prior to enrollment, %	5	5
UAC present at enrollment, %	43	36
UVC present at enrollment, %	48	32 [a]
RSS at enrollment, mean (SD)	2.0 (1.9)	2.0 (2.0)
Number of contiguous initial study drug courses		
1-course, %	70	72
2-courses, %	26	27
3-courses, %	4	1
PDA failed to close after initial drug treatment, %	57	62
Additional study drug given during feeding advance, %	10	7

Demographic and Risk variables:	**Total Population**	
	Fasting (*npo*) n=96	**Feeding n=81**
Ligation during feeding advance, %	18	21
Ligation during hospitalization, %	24	36 *b*
Age at 1st feeding-days, mean (SD)	4.9 (3.8)	3.5 (2.6) *a*
Maximum enteral volume prior to study-ml/kg/d, mean (SD)	12.3 (14.3)	15.6 (16.0)
Age at study entry-days, mean (SD)	6.4 (3.8)	6.6 (4.0)
Milk type-breast milk, %	83	84

a $p<0.05$

b $p<0.10$

Definitions: Betamethasone (>6hr), receipt of betamethasone more than 6 hours prior to delivery; *SGA*, birthweight <10th percentile for gestational age (22); *Age*, Postnatal age (where day of birth = 0); *RDS*, respiratory distress syndrome diagnosed by elevated oxygen requirement during the first 24 hrs and characteristic radiographic findings; *RSS at 24 hours*, Respiratory Severity Score: mean airway pressure x fraction of inspired oxygen, measured at 24 hours after birth; *UAC and UVC*, umbilical artery and venous catheters; *PDA failed to close after initial treatment*, defined as following treatment ductus arteriosus was still either (a) moderate-to-large, or (b) initially closed (or small) and reopened (and developed a moderate–to-large shunt again); *SD*, standard deviation

Table 5

Effect of "feeding" versus "fasting (*npo*)" on neonatal outcomes: univariate analyses

	Total Population	
	Fasting (*npo*) n=96	**Feeding n=81**
Feeding Related Outcomes:		
Age when taking 120 ml/k/d-days, mean (SD)	24.0 (9.6)	21.6 (8.7) *b*
Actual Number of days to reach 120 ml/k/d, mean (SD)	13.1 (7.8)	10.3 (6.6) *a*
Difference between Actual and Ideal number of days to reach 120 ml/k/d), mean (SD)	5.5 (7.1)	3.0 (6.3) *a*
Feeding advance delayed by feeding intolerance or NEC, %	40	24 *a*
Feeding advance delayed by "other" causes, %	44	59 *b*
NEC/perforation prior to reaching 120 ml/k/d, %	4	1
NEC/perforation ANY TIME during hospitalization, %	13	10
Age when central venous line removed-days, mean (SD)	30 (28)	27 (21)
infection during feeding advance, %	34	26
infection any time during hospitalization, %	45	44
Other Morbidities:		
ICH gr III or IV, %	7	5
PVL or hydrocephalus, %	7	6
BPD, %	36	56 *a*
ROP-treated, %	4	12 *b*
Death, %	7	5
Death or BPD, %	39	58 *a*
Death, NEC or BPD, %	43	61 *a*

a $p<0.05$

b $p<0.10$

Definitions: Age, Postnatal age (day of birth = 0 days); *Necrotizing enterocolitis*, Bell's classification ≥II (treated medically or surgically) and "spontaneous perforations" occurring before 7 days of life; *Infection*, any culture positive infection (bacteremia, pneumonia, urinary tract infection, meningitis); *ICH*, intracranial hemorrhage ≥ Grade III; *PVL*, cystic periventricular leukomalacia diagnosed by ultrasound; *BPD*, Bronchopulmonary Dysplasia: the need for supplemental oxygen to maintain oxygen saturation >90% at 36 weeks corrected age; *ROP*, stage 2 with plus disease or stage 3 treated with either laser or bevacizumab; *Feeding advance delayed by "other" causes*, percent of the population that had their feeding advance interrupted or delayed by one or more of the following causes: a) PDA ligation, b) sepsis workup, recurrent apneas, respiratory deterioration, c) hypotension requiring inotropes, or d) blood transfusions.

Table 7

Effect of "feeding" versus "fasting (*npo*)" on neonatal outcomes: adjusted odds ratios and correlation coefficients

	Total Population (n=177): Feeding versus Fasting (*npo*)	
	Outcome Variable	**p-value (95% CI)**
Feeding Related Outcomes:		
Age when taking 120 ml/k/d-days	**−3.38**	**0.009 * (−5.90 to −0.86)**
Actual number of days to reach 120 ml/k/d-days	**−3.64**	**0.001 * (−5.83 to −1.46)**
Difference between Actual and Ideal number of days to reach 120 ml/k/d-days	**−3.52**	**0.001 * (−5.56 to −1.48)**
Feeding advance delayed by feeding intolerance or NEC	0.53	0.103 (0.25 to 1.14)
Feeding advance delayed by "other" causes	1.80	0.151 (0.81 to 4.03)
NEC/perforation - prior to reaching 120 ml/k/d	1.60	0.450 (0.47 to 5.48)
NEC/perforation - ANY TIME during hospitalization	0.97	0.963 (0.28 to 3.37)
Age when central venous line removed - days	−5.23	0.193 (−13.13 to 2.66)
Infection during feeding advance	0.63	0.247 (0.29 to 1.37)
Other Morbidities:		
BPD	1.68	0.207 (0.75 to 3.77)
ROP-treated	2.28	0.277 (0.52 to 10.01)
Death	0.66	0.606 (0.14 to 3.16)
Death or BPD	1.74	0.167 (0.79 to 3.80)
Death, NEC or BPD	1.79	0.138 (0.83 to 3.88)

Analyses were performed by GEE (Generalized Estimating Equations) as described in Methods. The odds ratios (for binary outcomes), correlation coefficients (for continuous outcomes), p-values and 95% confidence intervals (CI) are reported. Predictive variables used in the models differed between the "*feeding*" and "*fasting (npo)*" groups in Table 1 with p-values ≤0.1. These included: multiple birth, RDS, Caucasian, umbilical venous catheter present at enrollment, PDA ligation during the hospitalization, and age when first fed. Note: when treated ROP was examined as an outcome, BPD was added to the other predictors in the GEE model.

* $p<0.05$