Enteral Feeding during Indomethacin and Ibuprofen Treatment of a Patent Ductus Arteriosus

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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/d) enteral feedings while receiving indomethacin or ibuprofen treatment for patent ductus arteriosus.

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/d, 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 weeks' mean ± 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 [*nil per os*]" group, n = 96: indomethacin 75%, ibuprofen 25%) during the drug administration period. Maximum daily enteral volumes before study entry were 14 ± 15 mL/kg/d. After drug treatment, infants randomized to the "feeding" arm required fewer days to reach the study's feeding volume end point (120 mL/kg/d). Although the enteral feeding end point was reached at an earlier postnatal age, the age at which central venous lines were removed did not differ between the 2 groups. There were no differences between the 2 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 end point if they were given "trophic" enteral feedings when they received indomethacin or ibuprofen treatments. *(J Pediatr 2013;163:406-11)*.

The prostaglandin synthase inhibitors indomethacin and ibuprofen are the only drugs licensed in the US 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 postprandial 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 [npo]) and received only intravenous nutrition during study drug administration. Currently, 85% of US 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

BPD	Bronchopulmonary dysplasia
NEC	Necrotizing enterocolitis
npo	Nil per os
PDA	Patent ductus arteriosus

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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 ≤60 mL/kg/d); 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 >60 mL/kg/d 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 (NEC) 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. 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. After the drug treatment assignment, infants were randomized to the study's feeding intervention: either "feeding" or "fasting (npo)" during the "study drug administration period" (definition given later). 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 retreatment 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 hours, respectively, if they were ≤1000 g at birth and <7 days old, or 0.2 mg/kg/dose for each of the 4 doses if they were >1000 g at birth or ≥7 days old). When ibuprofen was the study drug, infants received the same 3 doses of ibuprofen (independent of birth weight or postnatal age): 10, 5, and 5 mg/kg/dose at 0, 24, and 48 hours, respectively.

All infants had an echocardiogram and Doppler study performed before 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/d) was the primary end point 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 before the start of the trial. The feeding advance regimen specified the number of days (based on birth weight) of "trophic" feedings (15 mL/kg/d) 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

Table I. Feeding advance regimen

	mL/kg/d		
(A) Day of feeding	(B) Birth weight 401-700 g	(C) Birth weight 701-1000 g	(D) Birth weight 1001–1250 g
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 end point is achieved on the day infant takes 120 mL/kg/d.