Should Very Low Birth Weight Infants Receive Enteral Nutrition During Indomethacin or Ibuprofen Treatment of a Patent Ductus Arteriosus? A Multi-Center Randomized Controlled Trial.

Abstract

Approximately 25,000 premature infants per year receive indomethacin or ibuprofen during the newborn period to treat the symptoms of a patent ductus arteriosus. A problem that is inherent to this therapy is "what to do with enteral feedings during the time the infant is being treated with indomethacin or ibuprofen". Currently 85% of US neonatologists withhold feedings when using indomethacin or ibuprofen. However, recent evidence from animal and human studies, indicate that the practice of withholding infant feedings for several days may lead to subsequent feeding difficulties.

We think that feeding infants while receiving indomethacin or ibuprofen therapy will lessen the changes in intestinal permeability that occur with these drugs and will improve the infants' blood flow response to tube fed nutrition. We hypothesize that this will decrease the incidence of feeding intolerance and shorten the time before infants are able to tolerate full liquid tube feedings. If our hypothesis is confirmed, current clinical practice will be altered and new guidelines for infant nutrition will be established for infants being treated with indomethacin and ibuprofen

Study Design and Methods

Hypothesis

We hypothesize that feeding infants while they receive indomethacin or ibuprofen therapy will minimize the alterations in intestinal permeability that occur with these drugs and will improve the infants' hemodynamic response to enteral nutrition. We hypothesize that this will decrease the incidence of feeding intolerance and shorten the time before infants are able to tolerate full enteral nutrition.

Overview/Scope

This will be a prospective randomized, multi-center, controlled trial that will enroll infants from 401-1,250 g birth weight (delivered from $23^{1/7}$ – $30^{6/7}$ weeks gestation) who 1) are receiving or are ready to begin enteral feedings and 2) who are about to receive pharmacologic treatment to close their PDA. Exclusion criteria will be: contraindications for the use of indomethacin or ibuprofen, chromosomal anomalies, congenital or acquired gastrointestinal anomalies, prior episode of necrotizing enterocolitis, use of inotropic support for hypotension, or infants who are currently receiving greater than 60 ml/kg/day enteral feedings. (Note: umbilical artery or vein catheter placement will not serve as a basis for exclusion).

Study Procedures

Study infants will be randomized into **one of 4 study groups:**

A) indomethacin plus feeding
B) indomethacin without feeding
C) ibuprofen plus feeding
D) ibuprofen without feeding.

Randomization will be stratified by gestation 23-25 wks, 26-27 wks, 28-$30^{6/7}$ weeks and by center. Block randomization will occur by site. Research pharmacists will be supplied with sealed, numbered envelopes that will contain the assigned treatment. We will be able to mask the assignment of study drug (indomethacin or ibuprofen) from the clinical staff since the drug to be administered will be prepared by the research pharmacist in the same volume, and the same number of study drug doses (3 doses) will be administered to the randomized infants

during a 48-hour interval (indomethacin dosing: 0.2 mg/kg, 0.1 mg/kg and 0.1 mg/kg; ibuprofen dosing: 10 mg/kg, 5 mg/kg, and 5 mg/kg). From a practical aspect, we will not be able to mask the infant's assignment to the "feeding" or "withhold feeding" group.

The source of enteral nutrition, both during the administration of the study drug (indomethacin or ibuprofen) and during the interval until the primary outcome is achieved ("full enteral feeding" = 120 ml/kg/day), will be breast milk. A 20 cal/oz premature formula, currently in use at the individual study site, will be substituted for breast milk if mother's milk is unavailable. A standardized feeding advance regimen (that will be agreed upon prior to the start of the trial and instituted at each of the participating centers) will be followed to determine when enteral feeding can be introduced and the rate at which it can be increased. Because enteral feeding is the primary intervention for this proposal, the feeding regime needs to be directive rather than at the discretion of the clinicians. The unmasked nature of this randomized controlled trial also requires a directive feeding protocol to minimize bias in the management strategy. If the clinicians feel that they cannot comply with the proposed feeding regime, the infant under consideration will be excluded from the study.

The "***study drug period***" is defined as the interval of time between administration of the first dose of study drug (ibuprofen or indomethacin) and 24 hours after the last dose of study drug.

Feeding interventions during the "study drug period":

Infants randomized to one of the two "feeding" study groups (groups (A) or (C) above): will receive trophic enteral nutrition (15 ml/kg/day) during the *study drug period.*

Infants randomized to one of the two "withhold feeding" groups ((B) or (D) above): will be fasted during the *study drug period.*

After the *study drug period:* feedings will be returned to the pre-study volumes and advanced according to the standardized feeding advance regimen.

An echocardiogram of ductus arteriosus and descending aorta flow will be performed prior to receiving the first dose of study drug. Infants will be classified as having a moderate-to-large left-to-right ductus arteriosus shunt if they have at least 2 of the following echo criteria: 1) PDA diameter ≥ 1.5 mm at narrowest dimension (without the color signal on); 2) LA/Ao ratio (M-mode) ≥ 1.5:1 with unrestrictive flow (mean pressure gradient <8 mm); 3) Any degree of holodiastolic flow reversal in the descending aorta at the level of the diaphragmatic insertion. **The echocardiogram will be repeated 24 hours after the last dose of study drug to determine if there is any residual ductus patency and the size of the left-to-right shunt.** Both echocardiograms are part of the infant's routine clinical care. The clinical management of these infants will be at the discretion of the attending physicians. The only management controlled by protocol is the randomized selection of the PDA treatment drug and the feeding regimen. If the infant develops a symptomatic patent ductus arteriosus after the *study drug period*, the decision to ligate the ductus arteriosus will be left to the attending neonatologist.

Data Requirements

Demographic and clinical variables will be recorded to insure that the groups are comparable.

***Maternal Data*:** Age, race, gravidity, parity, pregnancy complications, antenatal steroid administration and antibiotics.

Neonatal Data: Gestation, birth weight, gender, race, inborn or outborn, Apgar at 1 and 5 minutes, resuscitation required, surfactant administered (number of doses), antibiotics, umbilical artery and vein catheterization (whether in place at the time of the study and duration in place), prior indomethacin prophylaxis, age at diagnosis of PDA, evaluation of left-to-right PDA shunt, age of first dose of study drug, PDA response to study drug, and need for PDA ligation.

The neonatal data will also include details about respiratory support and development of bronchopulmonary dysplasia: type of respiratory support, FIO_2, and ventilator settings will be used to calculate a respiratory severity score at 24 hours of age. Other respiratory outcomes include the length of ventilatory support, and duration of oxygen supplementation. Bronchopulmonary dysplasia will be diagnosed at 36 weeks postmenstrual age using an oxygen challenge test.

The enteral feeding data will include: age of initiation of feeding, number of days that infants were not offered enteral feeds (NPO) immediately after birth, the number of days with feeding interruptions (patient ordered NPO $\geq$12 consecutive hours within a 24 hour period) both before and after full enteral nutrition is achieved, and day of life on which full enteral nutrition was achieved.

Risks/Benefits

Both Indomethicin and Ibuprofen have some side effects. Kidney function may be affected during the administration for the PDA treatment but usually returns to normal after the medication is stopped. Bleeding problems have occurred with both medications. While Indomethacin and Ibuprofen have been shown in scientific studies to change the blood flow to the intestines and the intestinal walls, there are no studies that prove that feeding while on these medicines causes serious problems to the intestines.

It is very common for premature babies to have trouble with feedings because of the immaturity of their stomach and intestine. Feeding babies in the first few weeks of life may increase their risk of bloating, vomiting, constipation or even more serious problems like necrotizing entercolitis (NEC).

The infants will be assigned to treatment group by chance and the treatment the infant receives may prove to be less effective or to have more side effects than the other study treatment(s) or other available treatments.

Participation in this study may or may not make the infant's health better. It is possible that being in one group versus other may improve the baby's ability to tolerate feedings and reach the full amount of feedings more quickly.

Analysis

The primary endpoint of the study is the number of days to achieve "full enteral feeding". For each of study drugs, we will compare the outcomes in the feeding and fasting subgroups. The analysis of the number of days to achieve "full enteral feeding" will be a time to event analysis. We will assess if there is a need to transform data to correct for skewing. Categorical outcomes will be compared using a Chi-square test.

We will use logistic regression analysis to examine the independent effects of enteral nutrition (during study drug treatment) and both the presence and size of a persistent symptomatic PDA (after study drug treatment), on the Primary outcome and on the Other "secondary" outcomes.

Sample Size

The primary outcome is the number of days it takes to achieve "full enteral feeding" (defined as 120 ml/kg/day). Although a major concern is whether feeding during indomethacin/ibuprofen treatment will increase or decrease the incidence of necrotizing enterocolitis, it is not practical to design the study with this as the primary outcome because it would not be possible to enroll a sufficient number of patients in a reasonable period of time. Necrotizing enterocolitis occurs infrequently (7-10% incidence) in the population to be studied. Even with a one-side 5% level of significance, a total of 6000 patients (1500 in each of the 4 study groups) would need to be studied for the probability to be 80 percent that a significant difference in the incidence of necrotizing enterocolitis could be detected between enteral nutrition and fasting study groups. The Data Safety Monitoring Board will be charged to look at the incidence of necrotizing enterocolitis very carefully to try to detect an early increased trend in any of the study groups if it occurs.

Current available data from the University of California nursery indicates that VLBW infants weighing from 401-1500 at birth, who have a patent ductus arteriosus that requires treatment, achieve "full enteral feeding" (defined as 120 ml/kg/day) at 30±13 days after birth. Therefore, based on the assumption that the standard deviation of the time to achieve "full enteral feeding" is ±13 days, a total of 400 patients (100 in each of the 4 study groups) will need to be studied, for the probability to be 80 percent that a significant difference (of at least 4 days) could be detected between the enteral nutrition and fasting study groups (for each of the two drug treatment arms).

The actual number of infants to be enrolled in the trial will be determined during the trial, after 50% of the subjects have been enrolled. At that time, it will be possible to calculate the mean time (and standard deviation) to achieve "full enteral feeding" among the NON-fed study infants in our multi-center study population. These values can be used to calculate the actual number of subjects to be enrolled to detect the desired difference.

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