Official Title: Early Treatment Versus Delayed Conservative Treatment of the Patent Ductus Arteriosus in Preterm infants-a Multicenter Trial

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This prospective RCT was conducted between January 2014 and June 2017 at 17 international sites after obtaining Institutional Review Board approval at each site. Written informed parental consent was obtained before enrollment. Additional scientific review of the trial protocol was provided by the Gerber Foundation and the trial was registered with ClinicalTrials.gov (NCT01958320). Infants were eligible for the study if they met all three of the following conditions: 1) they were between 6-14 days old (day of birth = day 0) (if delivered between $23^{0/7}$ – $25^{6/7}$) or 8-14 days old (if delivered between $26^{0/7}$ – $27^{6/7}$), 2) had a moderate-to-large PDA (see below for criteria), and 3) were receiving greater than minimal respiratory support defined as either positive pressure ventilation, CPAP, or high flow nasal cannula support with >2 L/min cannula flow and FiO2 >0.25. Eligible infants were excluded from participation if they had received prior treatment with indomethacin or ibuprofen, had chromosomal anomalies, congenital or acquired gastrointestinal anomalies, prior episodes of necrotizing enterocolitis (NEC) or intestinal perforation, active pulmonary hemorrhage at the time of enrollment, or contraindications to the use of indomethacin or ibuprofen (e.g., hydrocortisone administration within preceding 24 hours, urine output < 1 ml/kg/h during preceding 8 hours, serum creatinine >1.6 mg/dl, platelet count <50, 000/mm^3, or abnormal coagulation studies). Sixteen of the 17 centers also excluded infants if they needed inotropic support for hypotension at the time of enrollment.

The echocardiographic studies included two dimensional imaging, M-mode, color flow mapping and Doppler interrogation as previously described. A moderate-to-large PDA was defined by a ductus internal diameter ≥ 1.5mm (or PDA:left pulmonary artery diameter ratio ≥0.5) and one or more of the following echocardiographic criteria: a) left atrium-to-aortic root (LA/Ao) ratio ≥1.6, b) ductus flow velocity ≤2.5m/sec or mean pressure gradient across the ductus ≤8mm, c) left pulmonary artery diastolic flow velocity > 0.2 m/sec, and/or d) reversed diastolic flow in the descending aorta. Ductus that failed to meet these criteria were considered to be "*constricted*" (small or closed) and not eligible for enrollment or treatment.

Randomization was stratified by gestational age ($23^{0/7}$-$25^{6/7}$ or $26^{0/7}$–$27^{6/7}$) and by center. Block randomization (in blocks of two) occurred at each site for each gestational age group with an allocation ratio of 1:1. Blinded randomization was assigned sequentially from sealed envelopes.

Our trial was a pragmatic RCT. Infants randomized to the Early Routine Treatment (Early Rx) group received either indomethacin, ibuprofen, or acetaminophen (with indomethacin backup if the PDA failed to constrict after the initial treatment). Since the drugs appear to have similar efficacies in closing the PDA, the choice of drug treatment was left to each center according to their standard practice. After completing the initial treatment, infants were followed to determine if they met eligibility criteria for "Rescue" treatment (see below). The "Rescue" treatment was the same drug treatment protocol used for the initial Early Rx at that site.

Infants randomized to the Conservative group did not receive any initial pharmacologic treatments to close the PDA. Study randomization was blinded, but treatment allocation by the medical team

was not blinded. Although this may have affected some of our outcome measures, we chose this approach since treatment blinding would have required unnecessary intravenous lines and therapy as well as additional blood tests for infants in the Conservative group.

Infants in both groups had repeat echocardiograms performed 7-10 days after randomization. Infants with a persistent moderate-to-large PDA after the first week were followed with frequent (every 7-14 days) echocardiograms to determine when ductus constriction occurred. Echocardiograms were performed until ductus closure or hospital discharge. Infants with a "constricted" (small or closed) ductus were examined daily for a change in clinical symptoms indicative of a reopened, moderate-to-large PDA (systolic murmur or hyperdynamic precordium). If either of these occurred, an echocardiogram was performed within 24 hours. In addition, routine echocardiograms were performed every 2-3 weeks until ductus closure or hospital discharge in infants with a "constricted" PDA.

Infants in the Conservative group, with a persistent moderate-to-large PDA after the first week, were eligible for rescue PDA drug treatment only if they met one or more of the following prespecified "Rescue" criteria: 1) Inotrope-dependent hypotension that required continuous dopamine support for at least 3 days (with no obvious cause, other than the moderate PDA, to explain the condition). Hypotension was defined as mean BP at least 2-to- 3 mm Hg below the infant's corrected postmenstrual age (in mm Hg). 2) Oliguria that persisted for at least 2 days with no obvious cause, other than the moderate PDA, to explain the condition. 3) Requirement for gavage feedings beyond 35 weeks corrected age due to increased work of breathing. 4) Respiratory support needed after the following postnatal ages that surpassed specific minimal ventilation and FiO2 requirements: >15 days (if still required intubation and FiO2 >0.30), >20 days (if still required intubation and FiO2 ≤0.30; or still required Nasal CPAP or Nasal ventilation and FiO2 >0.30), >30 days (if still required Nasal CPAP or Nasal ventilation and FiO2 0.25-0.30), and >45 days (if still required Nasal CPAP or Nasal ventilation and FiO2 <0.25).

The "Rescue" drug treatment for the Conservative group was the same drug treatment protocol used in the Early Rx group at that site. Neonatologists caring for infants in the Conservative group were not required or encouraged to treat infants who met "Rescue" criteria. Rather, the "Rescue" criteria served as the threshold or minimal criteria that were needed before infants in the Conservative group could be eligible for closure treatment. Infants in the Early Rx group, with persistent moderate-to-large PDAs after the first week, could receive rescue treatment at the clinician's judgment, whether or not they met "Rescue" criteria.

Surgical ligation was used only if pharmacologic agents had failed or were contraindicated. The decision to use rescue ligation was left to the attending neonatologist.

A Data Safety Monitoring Board performed regular interim analyses for both safety and efficacy and reviewed all serious adverse events.

Statistical analysis

Our trial was planned as a pilot exploratory trial. The primary outcome was "need for ligation or the need for PDA cardiology follow-up after discharge". We chose this outcome because we anticipated that with 200 patients we had sufficient power to detect a significant increase in the "need for ligation or the need for PDA cardiology follow-up after discharge" from an expected rate of 41% in

the Early Treatment group (based on prior data from University of California San Francisco - data not shown) to greater than 62% in the Conservative management group.

One of the main goals of our small, exploratory trial was to determine the incidence of serious neonatal morbidities in the two treatment groups so that hypotheses for future appropriately powered large scale RCTs could be generated. In our proposal to the funding agency we prespecified several secondary outcomes that we planned to examine and present descriptively because of the small size of the study population. These included the duration of intubation and respiratory support, the need for diuretic therapy, the time before full enteral intake was achieved, the duration of gavage feeding, the average daily weight gain, the incidence of persistent moderate-to-large PDA shunt 10 days after enrollment, the incidence of rescue treatment eligibility criteria met, and the incidence of serious neonatal morbidities (NEC, BPD, Death, BPD/Death). The incidence of several other important morbidities and therapies were also examined as additional "exploratory analyses".

All analyses were based on the infants' group randomization assignments. STATA (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP) was used for all statistical analysis. Chi-Squared tests were used to compare the treatment groups for categorical variables. For continuous variables, Student's t-tests were used to compare groups for parametric variables and Wilcoxon rank sum tests to compare groups for non-parametric variables. Logistic regression was used to determine the risk ratio and risk difference for the predictor variable (treatment group) and the various outcome measures. Linear regression and Poisson regression were used to determine the mean difference between the groups where appropriate. Generalized estimating equations were used to determine if the infants' gestational age modified the effects of treatment assignment on the various outcomes of interest.

Despite randomization, infants in the two treatment groups differed in two of the prenatal and neonatal demographic variables (multiple birth and early onset bacteremia). Therefore, we created additional multivariate models designed to examine the effects of the treatment assignment on neonatal outcomes. The adjusted multivariate models used generalized estimating equations to account for clustering within center, and included gestational age, multiple births, early onset bacteremia, and the variable of interest (treatment assignment). An interaction term between treatment assignment and gestational age was also included in the model for a particular outcome if the interaction between treatment assignment and gestational age for that outcome reached a level of significance of $p<0.15$.