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Antenatal effects of indomethacin on treatment of very premature infants with PDAs

A. Study Purpose and Rationale

The incidence of PDA is significantly higher in preterm infants, occurring in 1 and 3 infants with very low birthweight (<1500g) versus 57 per 100,000 of term infants (1). A persistent PDA in the premature population places infants at risk for the detrimental sequelae of left to right shunting in the cardiopulmonary circulation, including pulmonary edema, decreased lung compliance, prolonged ventilation, and cardiopulmonary compromise. Infants with PDAs are at greater risk for BPD, CLD, NEC, IVH, and death (2). Currently, there is a wide variability amongst institutions in management of PDA, which can be attributed to the lack of prospective randomized controlled studies investigating long term effects of medical (indomethacin/ibuprofen) treatment versus conservative management (fluid restriction, no NSAIDs). A Cochrane review conducted in 2010 showed that indomethacin treatment decreases incidence of symptomatic PDA on echo, need for surgical ligation, and grade III and IV IVH. However, there was no benefit in overall mortality, incidence of NEC, pulmonary or neurodevelopmental outcomes. The article concluded that management of PDA in premature infants should be considered on an individual basis (3).

Current trends in treatment of PDA in premature infants suggest that 60-70% of infants 28 WGA or under require medical and/or surgical treatment (4). Primary ductal closure is achieved in 60-80% of infants after primary treatment with indomethacin, and secondary closure is achieved in an additional 44% requiring a second course of treatment (5). The remaining population requires additional treatment methods, including surgical ligation, to treat PDA. Determining risk factors that contribute to the success or failure of medical treatment will help aid in decisions about management of this population. This is especially important given that medical treatment with indomethacin is not without its own risks and a large proportion of PDAs close spontaneously. In a recent cohort of VLBW infants with PDAs who were not treated, 85% experienced PDA closure by the time of hospital discharge (6).

Although studies are conflicting, antenatal exposure to indomethacin has been linked to increased incidence of PDA, increased severity of PDA (7), and increased need for surgical ligation in the setting of medical treatment failure (8). Indomethacin does cross the placenta and cause constriction of the ductus arteriosus in utero. Studies in animal models showed a decrease in PDA constrictiveness after initial ductal constriction in utero, suggesting decreased sensitivity and limited response to indomethacin (9). This could explain the findings above, associating indomethacin exposure in utero with PDA treatment failure. The majority of these studies were conducted several years ago (1990s-early2000s) when neonatal practices differed significantly, and with small sample sizes. Our study will pose this question in a large cohort and more current population.

B. Study Design

This study will be a retrospective chart review of preexisting data from the medical records of preterm infants admitted to the neonatal intensive care unit (NICU) of New York Presbyterian Hospital. The NICU is located on the seventh floor of the main children's hospital tower building. Eligible subjects will be preterm infants born at or less than 28 weeks of gestation in the period from 01/01/2008 through 12/31/2014 who had echocardiographic diagnosis of a moderate to large patent ductus arteriosus (PDA) with a left to right shunt. Data will be collected from the maternal and newborn electronic medical records (EMR) of each eligible patient.

Exclusion criteria will be outborn infants, infants transferred to another institution within first month of life, infants with small or restrictive PDA or PDA with persistent right to left shunt or bidirectional shunt with PPHN, major congenital anomalies, major congenital heart disease (non-PDA).

The primary outcomes will be the incidence of infants requiring medical treatment (indomethacin) with moderate to large PDA's in the first month of life, and the incidence of failure of medical treatment requiring surgical ligation. Clinical characteristics of infants with and without treatment will be compared to explore confounding factors that would increase severity of PDA and treatment failure. These will include demographic characteristics, infections leading to respiratory distress, exposure to antenatal steroids, and exposure to tocolysis (indomethacin and other).

C. Statistical Analysis

Univariate analysis will be performed using the chi-square for qualitative variables, to assess for an effect on antenatal indomethacin exposure on severity of PDA requiring treatment, and treatment failure requiring surgical ligation. Multivariate analysis will be performed using logistic regression model to assess for risk factors leading to PDA severity and treatment failure.

A P value of 0.05 or less will be considered significant.

We are anticipating 500 eligible infants for total enrollment and total 210 accrued infants. If we assumed that about 50% of our sample is treated with indomethacin, and 60% of that sample size was exposed to indomethacin in the antenatal period, we need p2 <0.39, or 39% or less incidence of antenatal indomethacin exposure in the non-treated group to show clinical significance difference at P=0.05 with 80% power.

In the population that requires surgical ligation, we would assume that about 24% of those treated with indomethacin fail medical management. If we assume 85% of this population was treated with indomethacin, we could show P2 <0.56 with clinical significance at difference P = 0.05 and 80% power.

D. Study Procedure

Retrospective analysis of existing clinical and laboratory data of preterm infants admitted to the neonatal intensive care unit at New York Presbyterian- Columbia Hospital

E. Recruitment and Consent

Study patients will be selected from existing databases and EMR based on gestational age and PDA status. This is a retrospective study. This study will apply for waiver of consent.

F. Research Aim

Primary Aim: Does antenatal indomethacin exposure predict: (1) severity of PDA leading to need for treatment and (2) incidence of medical treatment failure in very premature infants with PDAs?

G. Potential Risks

No associated risks except for potential loss of confidentiality. No new information will be obtained. We have put together all procedures necessary to protect the confidentiality of all subjects.

H. Potential Benefits

No direct benefit to participants given the retrospective nature of the study. The study results may be able to provide help guiding physicians in weighing risks versus benefits of using indomethacin to treat a large PDA.

I. Data and Safety Monitoring

No new data will be formulated from this study. It is a retrospective review and analysis of existing data in the medical records of infants who have received their clinical care prior to the initiation of the study.

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