Preconference materials for Cochrane Neonatal April 2019 Webinar

Case 1: A comparison of ibuprofen and indomethacin for closure of patent ducturs arteriousus. Van Overmeire and colleagues. N Engl J Med. 2000;343:674-81.

Indomethacin is the conventional treatment for patent ductus arteriosus in preterm infants. However, its use is associated with various side effects. In a prospective study, we compared ibuprofen and indomethacin with regard to efficacy and safety for the early treatment of patent ductus arteriosus in preterm infants. We studied 148 infants (gestational age, 24 to 32 weeks) who had the respiratory distress syndrome and an echocardiographically confirmed patent ductus arteriosus. The infants were randomly assigned at five neonatal intensive care centers to receive three intravenous doses of either indomethacin or ibuprofen, starting on the third day of life. The rate of ductal closure, the need for additional treatment, side effects, complications, and the infants' clinical course were recorded. The infants at each unit were randomly assigned to a treatment group by means of cards in sealed opaque envelopes. Each infant received three doses of either indomethacin (Indocid I.V., Merck, West Point, Pa.; 0.2 mg per kilogram at 12-hour intervals) or ibuprofen (an initial dose of 10 mg per kilogram, followed by two doses of 5 mg per kilogram each, after 24 and 48 hours). We calculated that a study group of 140 neonates would be necessary for the study to be able to detect a difference of at least 20 percentage points in the closure rate between the ibuprofen and indomethacin groups, assuming a closure rate of 80 percent with indomethacin, with a P value of 0.05 and a power of 80 percent. The t-test, Mann–Whitney U test, and chi-square test or Fisher's exact test were used to compare continuous normally distributed data, nonparametric continuous data, and categorical data, respectively. All reported P values are two-tailed. The rate of ductal closure was similar with the two treatments: ductal closure occurred in 49 of 74 infants given indomethacin (66 percent), and in 52 of 74 given ibuprofen (70 percent) (relative risk, 0.94; 95 percent confidence interval, 0.76 to 1.17; P=0.41). The numbers of infants who needed a second pharmacologic treatment or surgical ductal ligation did not differ significantly between the two groups. Oliguria occurred in 5 infants treated with ibuprofen and in 14 treated with indomethacin (P=0.03). There were no significant differences with respect to other side effects or complications.

Case 2: Effects of indomethacin in premature infants with patent ductus arteriosus: results of a national collaborative study. Gersony and colleagues. J Pediatr. 1983;102(6):895-906.

An infant was considered to have a significant PDA when various combinations of murmurs, other cardiopulmonary abnormalities, and laboratory findings were present. First-order clinical criteria included the presence of a continuous murmur, a systolic murmur, or when no murmur was present, need for ventilatory support for at least 48 hours. Given one of these, the infant was evaluated for the presence of second-order criteria, which consisted of clinical signs such as hyperactive precordium, increased pulse pressure (or bounding pulses), tachycardia (heart rate > 170 bpm), tachypnea (respiratory rate > 70/min), hepatomegaly (> 3 cm below right costal margin), and the need for varying levels of ventilatory support, as well as noninvasive findings: LA/AO by echocardiography > 1.15 and cardiomegaly with pulmonary plethora on chest radiograph.

Case 3: Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. Schmidt and colleagues. N Engl J Med. 2001. 2001;344(26):1966-72.

Schmidt and colleagues randomly assigned 1202 extremely low birth weight infants to receive either indomethacin (0.1 mg/kg) or placebo intravenously once daily for three days. The primary outcome was a composite of death, cerebral palsy, cognitive delay, deafness, and blindness at a corrected age of 18 months. Secondary short-term outcomes were patent ductus arteriosus, pulmonary hemorrhage, chronic lung disease, ultrasonographic evidence of intracranial abnormalities, necrotizing enterocolitis, and retinopathy. Secondary long-term outcomes were hydrocephalus necessitating the placement of a shunt, seizure disorder, and microcephaly within the same time frame. A computer-generated randomization scheme was used to assign the infants (in random blocks of two or four) to treatment groups in a 1:1 ratio. Randomization was stratified according to birth weight (500 to 749 grams vs. 750 to 999 grams) and according to study center. Each study pharmacist received a binder containing the sequence of treatment-group assignments for each birth-weight stratum from a statistician at the coordinating center who was not otherwise involved in the trial. At each study center, access to the binder was restricted to selected pharmacy personnel. The infants received either indomethacin, 0.1 mg per kilogram of body weight (Indocid P.D.A., Merck Frosst, Kirkland, Que., Canada, and Merck, West Point, Pa.), or an equivalent volume of normal saline. Three doses were given at 24-hour intervals. Each dose was infused intravenously over a period of 20 minutes. Since even a small volume of reconstituted indomethacin has a slightly yellow tinge, all syringes were partially masked with yellow tape.

Case 4: Efficacy and safety of intravenous paracetamol in comparison to ibuprofen for the treatment of patent ductus arteriosus in preterm infants: study protocol for a randomized control trial. Trials. Dani and colleagues. 2016;17:182.

We present the design of a randomized, multicenter, controlled study, whose aim is to assess the effectiveness and safety of intravenous paracetamol in comparison to intravenous ibuprofen for the treatment of PDA in preterm infants. A total of 110 infants born at 25+0 to 31+6 weeks of gestational age will be enrolled and randomized to receive paracetamol or ibuprofen (55 patients per group) starting at 24 to 72 h of life. The primary endpoint of the study is the comparison of the PDA closing rate observed after a 3-day course with paracetamol or ibuprofen. The secondary endpoints include the closure rate of PDA after the second course of treatment with ibuprofen, the re-opening rate of the PDA, the incidence of surgical ligation, and the occurrence of adverse effects. This is a randomized, open-label, parallel-group, ibuprofen-controlled, multicenter, prospective study, involving five Neonatal Intensive Care Units (NICU) in Italy. The trial was designed following the SPIRIT 2013 statement. The study was planned as a noninferiority trial. A total of 110 patients are expected to be enrolled in the study and to be randomized to either the paracetamol or ibuprofen group (55 patients per group). The study was conceived as a superiority trial aimed to demonstrate the superiority of paracetamol over ibuprofen on the primary efficacy endpoint of closing PDA after a 3-day course. Assuming a 25% ibuprofen failure rate in closing PDA and a 5% paracetamol failure rate (improvement of 20%), we used the $\chi 2$ test to calculate that a sample size of 49 evaluable patients per group will

be necessary to determine a statistically significant decrease of 20% in the failure rate in the paracetamol group at a two-sided alpha level of 5% and with a power of 80%.

Case 5: Patent ductus arteriosus in preterm infants. Benitz; Committee on Fetus and Newborn; American Academy of Pediatrics. Pediatrics. 2016;137(1).

Despite a large body of basic science and clinical research and clinical experience with thousands of infants over nearly 6 decades,[1] there is still uncertainty and controversy about the significance, evaluation, and management of patent ductus arteriosus in preterm infants, resulting in substantial heterogeneity in clinical practice. The purpose of this clinical report is to summarize the evidence available to guide evaluation and treatment of preterm infants with prolonged ductal patency in the first few weeks after birth.