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RESEARCH NEWS

Does Indomethacin Prophylaxis Benefit Extremely Low Birth Weight Infants? Results of a Placebo-Controlled Multicenter Trial

A review of: Schmidt B, Davis P, Moddemann D, Ohlsson A *et al*. 2001 Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med 344:1966–1972

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THE ADVANCES IN perinatal care have substantially reduced the mortality of extremely low-birth-weight (ELBW; <1000 g) infants. However, it has been difficult to reduce the proportion of impaired survivors. In an effort to reduce these impairments, some neonatologists administer low-dose indomethacin prophylaxis to ELBW infants within the first hours after birth. This intervention reduces the incidence of not only patent ductus arteriosus but also intraventricular or periventricular hemorrhage (as diagnosed using cranial sonography) (1). However, indomethacin prophylaxis has not been widely used because of concern that it might increase ischemic brain injury, retinopathy of prematurity, necrotizing enterocolitis, or gastrointestinal perforation.

The trial published by Schmidt and colleagues evaluated whether indomethacin prophylaxis increases the survival of ELBW infants without neurosensory impairment. A total of 1202 infants in 32 centers were randomized to receive indomethacin at a dose of 0.1 mg per kilogram or placebo (saline) given 3 times at 24-hour intervals starting before 12 hours of age. Caregivers, investigators, and parents were masked to treatment group. The two groups were similar at randomization, and outcome at 18-21 months was determined for a high proportion (95%) of all infants enrolled. As someone who participated in performing the trial but not in its design, analysis, or publication, I view this trial to be one that meets strict methodological criteria (2).

As expected, a significantly lower percentage of the indomethacin group than the placebo group experienced severe intraventricular hemorrhage (9 *versus*13%), patent ductus arteriosus (24 *versus* 50%), or surgery to ligate the ductus arteriosus (7 *versus* 12%). However, there were no other significant differences and no evidence of improved neurosensory or pulmonary outcomes. The primary outcome–death or impairment (defined as death, cerebral palsy, Bayley II Mental Developmental Index <70; bilateral blindness, or hearing loss requiring amplification)–occurred in 47% of the indomethacin group and 46% of the placebo group. Odds ratios >1.0 (indicating no tendency for a more favorable outcome in the indomethacin group) were noted for each component of the primary outcome and for a variety of secondary outcomes, including shunt-treated hydrocephalus, oxygen administration at 36 weeks postmenstrual age, oxygen administration after discharge home, bilateral retinopathy, necrotizing enterocolitis, and gastrointestinal perforation.

Why did indomethacin prophylaxis fail to improve neurosensory outcome? Indomethacin might have benefits that would be identified only with longer follow-up, as suggested by subgroup analyses of a smaller trial by Ment and colleagues (3). With the relatively low current incidence of severe (Grade 3 or 4) sonographic abnormalities, indomethacin prophylaxis resulted in only a small absolute reduction in these abnormalities (from 13 to 9%). This would limit the benefits associated with improved sonographic findings. Another potential explanation is that the usual relationship of sonographic findings to neuropathology and to prognosis is altered by administration of a drug like indomethacin that influences cerebral blood flow or metabolism. This issue has apparently not been considered in validation studies of cranial sonography.

What conclusions should be drawn from this study? The study may be interpreted as showing that Indomethacin prophylaxis reduces the need for ductal ligation without imposing serious hazards. However, it is unclear whether indomethacin reduced the number of infants who either died or underwent surgery of any kind (including shunt insertions for hydrocephalus, laparotomy for necrotizing enterocolitis, surgical procedures for retinopathy of prematurity). In the absence of clear benefit, indomethacin prophylaxis might be limited to centers where the frequency or morbidity of ductal ligations is unusually high. Whether or not indomethacin prophylaxis is used, the development of new treatment methods is needed to substantially reduce the high rate of adverse outcomes in ELBW infants.

1. Fowlie PW 2000 Intravenous indomethacin for preventing mortality and morbidity in very low birth weight infants (Cochrane review) In: The Cochrane Library, issue 4. Oxford, England: Update Software, (software)
2. Moher D, Schulz KF, Altman D for the Consort Group 2001 The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 285:1987–1991
3. Ment LR, Vohr B, Allan W, Westerveld M, Sparrow SS, Schneider KC, Katz KH, Duncan CC, Makuch RW 2001 Outcome of Children in the indomethacin intraventricular hemorrhage prevention trial. Pediatrics 105:485–491

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