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## *Selected Summaries*

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### **Neurodevelopmental Outcome With Early Indomethacin**

[Ment LR, Vohr B, Oh W, et al. Neurodevelopment outcome at 36 months' corrected age of preterm infants in the Multicenter Indomethacin Intraventricular Hemorrhage Prevention Trial. *Pediatrics* 1996, 98: 714-718.]

Preterm infants with parenchymal involvement of intraventricular hemorrhage (IVH) are thought to be at particularly high risk for neurodevelopmental handicaps; mental retardation, seizures and cerebral palsy. Concern about the neurodevelopmental outcomes of these patients has prompted multiple pharmacologic intervention trials to prevent IVH.

Because previous clinical trials had suggested that indomethacin lowered the incidence of IVH in very low birth weight preterm infants, a prospective, randomized, placebo-controlled trial to evaluate the use of low-dose indomethacin for the prevention of neonatal IVH was begun by three institutions in September 1989(1). This study demonstrated that indomethacin significantly lowered the incidence and severity of IVH, particularly parenchymal involvement of hemorrhage, in very low birth weight infants with no evidence of IVH in the first 6 postnatal hours. However, numerous studies using near-infrared spectroscopy and Doppler measurements of cerebral blood flow suggested that indomethacin lowered cerebral blood flow and might thus increase the risk of developmental handicaps in these frequently critically ill infants. All surviving infants were enrolled in a neurodevelopmental

follow-up program and evaluated at 36 months' corrected age (CA) to test the hypothesis that the early administration of low-dose indomethacin would not increase the risk of neurodevelopmental handicaps in this vulnerable very low birth weight population.

Authors enrolled 431 neonates of 600 to 1250 g birth weight with no IVH at 6 to 12 hours in a randomized, prospective trial to determine whether low-dose indomethacin would prevent IVH. *A priori* neurodevelopmental follow-up examinations, including the Stanford-Biriet Intelligence Scale and Peabody Picture Vocabulary Test-Revised and standard neurologic examination were planned at 36 months' CA.

Three hundred eighty-four of the 431 infants survived and 343 (89%) children were examined at 36 months' CA. Thirteen (8%) of the 166 infants who received indomethacin and 14 (8%) of 167 infants receiving the placebo were found to have cerebral palsy. There were no differences in the incidence of deafness or blindness between the two groups. The IQ scores in the two groups were comparable.

The authors conclude that indomethacin administered at 6 to 12 hours as prophylaxis against IVH in very low birth weight infants does not result in adverse cognitive or motor outcomes at 36 months' CA.

#### **Comments**

Additional benefits of indomethacin prophylaxis include closure of PDA. A recent study had suggested that earlier administration of indomethacin is associated with significantly less ductal reopening(2).

Antenatal steroids are now routinely

prescribed for preterm labor and offer a number of benefits. Even among these preterms it has been shown that indomethacin offered additional benefit. The incidence of IVH was only 3% compared with 13% for antenatally steroid exposed infants who received a placebo instead of indomethacin(3).

If there are so many benefits, the obvious question is: "Should indomethacin be administered routinely for IVH prevention?" In a commentary(4), it has been emphasised that before this question can be answered, several issues must be addressed, if not resolved. Who should receive prophylactic therapy? Obviously, those infants at high risk for developing IVH. However, it is not adequate to define the high risk infants based solely on birth weight or gestational age. Should prophylaxis be limited to those requiring ventilator support? How about the premature infants without antenatal steroid exposure? The criteria as to who should receive prophylaxis need to be established; if not, a large number of infants would be treated unnecessarily.

Further, considerable variation exists among trials as to drug administration. Studies differ in dosage of indomethacin, dose interval, number of doses, days of therapy, and duration of infusion. Whether a head ultrasound scan is needed prior to initiation of prophylaxis is another unresolved issue.

The declining incidence of IVH over the years and the fact that indomethacin therapy is not without its share of complications have dampened enthusiasm for routine prophylaxis. From a meta-analysis(5), it is estimated that treating 100 infants will result in 4 fewer infants with grades 3 or 4 IVH, at the expense of 5 "extra" infants with renal complications and perhaps an increased number with necrotizing

enterocolitis. Further, indomethacin prophylaxis has not decreased pulmonary morbidity. It is recommended that for now pending additional data, prophylaxis should probably be limited to infants weighing < 1250 g, requiring ventilator support, whose blood gases and blood pressure are within clinically acceptable range, and who have an absence of contraindications (obvious bleeding, high creatinine, and low platelet count)(4).

Another related question is - Can indomethacin be administered to the mother when premature delivery is expected? Well, indomethacin has been used as a tocolytic agent and found to be effective. However, there is a risk to the fetus secondary to ductal closure if the delivery does get postponed.

**Krishan Chugh,**

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