Indomethacin and Retinopathy of Prematurity (ROP) in Infants with Patent Ductus Arteriosus (PDA)

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Flower et al (1), reported that aspirin treated, oxygen-exposed beagle puppies developed retinopathy of significantly greater severity than their unmedicated, oxygen-exposed littermates. Direct ophthalmoscopic observations indicated that whereas sustained oxygen breathing produced retinal vasoconstriction in unmedicated puppies, retinal vessels of aspirin treated littermates became dilated or remained unchanged. The authors concluded that retinal vasoconstriction, if viewed as physiologic and protective, may be abolished by a prostaglandin synthetase inhibitor such as aspirin, thereby allowing a free flow of hyperoxic blood into retinal tissue causing oxygen damage. Prompted by this observation, we reviewed our experience of the past 8 years to determine whether the use of indomethacin, a potent prostaglandin synthetase inhibitor for closure of PDA, made any difference in the incidence and severity of ROP in extremely low birth weight infants.

Material & Method: We reviewed our experience in 75 PDA infants of less than 1001 gm at birth who survived for more than 8 weeks during the past 8 years. All infants below this weight limit were considered to have PDA. Symptomatic PDA was defined by the presence of a systolic murmur, bounding pulses, hyperactive precordium, wide pulse pressure, increased pulmonary markings and a left atrial to aortic root ratio of more than 1.3 determined by echocardiogram. The criteria for indomethacin treatment included one or more of the following: 1. congestive heart failure, 2. inability to wean from the respirator, 3. inability to provide sufficient calories for growth because of prolonged requirement of fluid restriction. Indomethacin was given via nasogastric tube at a dose of 0.2 mg/kg/dose, subsequent doses were given as indicated every 8 hours. No more than 6 doses were given to a single patient. The following information was extracted from retrospective review of patient's records: 1. gestational age, 2. birth weight, 3. duration of arterial oxygen tension (PaO_2) or transcutaneous oxygen tension ($TcPO_2$) more than 100 torr, 4. duration of oxygen therapy, 5. duration of arterial or capillary CO_2 tension (PCO_2) more than 50 torr and 6. duration of mechanical ventilation.

Indirect ophthalmoscopy was performed by a pediatric ophthalmologist who had no knowledge of indomethacin treatment at 4 to 6 weeks of age and a week before discharge. Infants found to have retinal pathology were repeatedly examined during their hospital stay and in high risk follow-up clinic as an outpatient.

Results. Of the 75 patients, 29 had asymptomatic PDA, 20 had symtomatic PDA but not treated with indomethacin and 26 patients

were symptomatic and had been treated with indomethacin. (Table I) None of asymptomatic PDA infants developed ROP. Fifteen percent (3/15) of the symptomatic PDA infants who had not been treated with indomethacin developed mild ROP. None progressed to cicatricial ROP (cROP). Thirty-five percent (9/26) of the indomethacin treated PDA infants developed ROP; more than half progressed to cicatricial changes (Grade III to V) of which 3 were blind. The difference in the incidence and severity of ROP is statistically significant among the three groups of infants.

Comparing the group of infants who developed ROP with those who did not, there was no significant difference in birth weight, gestational age, length of mechanical ventilation and duration of PCO_2 over 50 torr. Infants who developed ROP received significantly longer O_2 therapy and were exposed to longer hours of hyperoxemia (PO_2 <100 torr).

Conclusion: We believe that the pathogenesis of ROP is multifactorial in nature and it is the interactions among factors rather than any single factor alone which are important. Our study shows that indomethacin treatment may be one of those factors contributing to the development of ROP.

Table I. Indomethacin & ROP in Infants <1000 gm with PDA

PDA	NO	ROP(%)	cROP(%)	Blind(%)
Asymptomatic	29	0 (0)	0 (0)	0
Symptomatic	20	3 (15)	0 (0)	0
Sympt+Indomethacin	26	9 (35)	5 (19)	3 (12)
X^2		12.24	10.1	5.89
P		<0.01	<0.01	<0.02

Table II ROP AND RISK FACTORS

	ROP	No ROP	P*
No patient	9	27	
Gestational age(wks)	27±1.4	27±1.0	NS
Birthweight(gm)	853±121	887±93	NS
Indomethacin R_x(%)	6 (66%)	3 (11.1%)	<0.005**
PO_2>100 torr (hrs)	11.6±6.6	6.0±11	<0.02
O_2 therapy (days)	50±26	37±41	<0.05
PCO_2 >50 torr (days)	144±218	63±113	NS
IMV (days)	17±8.5	21±25	NS

*Mann Whitney Test
**Fisher Exact Test

References: 1. Flower RW et al. Ped. Res. 1981, 15:1293, 2. Feman & Reinecke, Hand Book of Ped. Ophthal, Grune & Stratten 1978.
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