

Use of indomethacin and its relationship to retinopathy of prematurity in very low birthweight infants

RENATO S PROCIANOY, JOSEPH A GARCIA-PRATS, HELEN M HITTNER, JAMES M ADAMS, AND ARNOLD J RUDOLPH

Department of Pediatrics and Department of Ophthalmology, Baylor College of Medicine, and the Neonatology Service of Texas Children's Hospital, Houston, Texas, USA

SUMMARY The relationship between the use of indomethacin, a prostaglandin inhibitor, for closure of patent ductus arteriosus (PDA) and the occurrence of retinopathy of prematurity was investigated retrospectively. 63 preterm infants ≤ 1500 g who were ≤ 32 weeks' gestational age, appropriate weight for gestational age, with a diagnosis of PDA, and admitted during the first 24 hours of life were studied. Diagnosis of retinopathy was made by retinal examination when each infant was about 4 weeks. Diagnosis of PDA was made by clinical, radiological, and echocardiographic findings. 15 patients were treated with indomethacin because of severe congestive heart failure. There were no differences between gestational ages, birthweights, duration of oxygen therapy, or incidence of retinopathy in treated and untreated patients. We suggest that the use of indomethacin for PDA closure does not increase the incidence of retinopathy in very low birthweight infants.

Indomethacin, an inhibitor of prostaglandin synthetase, has been used for closure of patent ductus arteriosus (PDA) in low birthweight infants.¹⁻² However its effect on other blood vessels, especially those in the retinal circulation, is unknown. There has been discussion about the possibility of an increased incidence of retinopathy of prematurity (ROP) in indomethacin-treated preterm infants, because of the similarity between the retinal vessels and the ductus arteriosus in their sensitivity to oxygen.³ ROP is a vascular or circulatory disorder of the developing retinal arteries caused by vasoconstriction,⁴ and the effect of indomethacin on the retinal circulation of preterm infants is not known. Our study was undertaken to determine whether an association exists between ROP and use of indomethacin for closure of PDA in very low birthweight infants.

Baylor College of Medicine, Houston
Department of Pediatrics

RENATO S PROCIANOY, post doctoral fellow in neonatal-perinatal medicine

JOSEPH A GARCIA-PRATS, assistant professor of pediatrics

JAMES M ADAMS, assistant professor of pediatrics

ARNOLD J RUDOLPH, professor of pediatrics

Department of Ophthalmology

HELEN M HITTNER, clinical assistant professor of ophthalmology

Material and methods

We studied retrospectively all newborn infants admitted in the first 24 hours of life to the neonatal intensive care unit at Texas Children's Hospital from January 1976 to June 1978. The infants studied fulfilled the following criteria: birthweight ≤ 1500 g, gestational age ≤ 32 weeks, appropriate for gestational age,⁵ diagnosis of PDA requiring treatment of at least fluid restriction, and survival for the first month of life.

The following data were abstracted from charts of patients enrolled in the study: birthweight, gestational age, oxygen exposure, use of exchange transfusion, presence or absence of hyaline membrane disease (HMD), ROP, intraventricular haemorrhage (IVH), and PDA.

Gestational age was determined by maternal dates and confirmed by physical examination.⁶ If there was a difference of more than 2 weeks between the physical findings and the mother's dates, the clinical assessment was adopted. The diagnosis of PDA was based on the presence of a systolic murmur, bounding pulses, hyperactive precordium, wide pulse pressure, enlarged heart size on x-ray, and increased left atrial/aortic root ratio (>1.3) on the echocardiogram. HMD was diagnosed by the

presence of expiratory grunting, chest retraction, maximum oxygen requirement $\geq 50\%$, and the presence of reticulogranular pattern on the x-ray. The diagnosis of IVH was made by the clinical findings of cardiovascular collapse, sudden drop in haematocrit, presence of full fontanelle, bloody cerebrospinal fluid tap which did not clear, seizures, apnoea, and posthaemorrhagic-hydrocephalus, as well as by computerised axial tomography (CAT) scan during the acute phase of the IVH (first 10 days of life). The diagnosis of ROP was made by one of us by indirect ophthalmoscopy from about 4 weeks of age. ROP was classified into grades 1 to 4 in both the active (aROP) and the cicatricial (cROP) phases.⁷⁻⁸ Follow-up examinations were performed as necessary.

Duration of treatment with oxygen was calculated by reviewing the patient's chart. For each patient the amount of oxygen received was recorded hourly and the mode of delivery was noted. All patients having oxygen therapy had central blood-gases checked as frequently as judged necessary and Pao_2 was maintained below 70 mmHg (9.3 kPa).

One of the following criteria had to be met before the use of indomethacin for closure of PDA: (a) inability to wean from the ventilator, (b) inability to provide adequate nutrition for growth, or (c) need for reinitiation of ventilatory support because of congestive heart failure. Indomethacin was given orally, 0.1 mg/kg, three times a day every 8 hours. Student's *t* test and χ^2 analysis were used to interpret the data.

Results

We studied 63 newborn infants with PDA. 15 were treated with indomethacin (group 1) and 48 were not (group 2). Of those 63, 31 developed aROP and 9 of them developed cROP, 3 with complete retinal detachment.

Table Data (mean \pm SD) on 63 newborn infants with patent ductus arteriosus

	Group 1, n=15 (treated patients)	Group 2, n=48 (untreated patients)
Birthweight (g)	1120 \pm 246	1150 \pm 252
Gestational age (weeks)	28.36 \pm 2.0	29.33 \pm 1.63
Duration of treatment with oxygen (hours)	776 \pm 660	441 \pm 603
Exchange transfusion	6(40)	6(13)*
Hyaline membrane disease	13(87)	25(52)*
Intraventricular haemorrhage	6(40)	16(34)
Retinopathy of prematurity		
Active	8(53)	23(48)
Cicatricial	2(13)	7(15)

* $P < 0.05$.

Percentages are given in parentheses.

The mean age at treatment was 11.3 days. The rate of success, evaluated by the disappearance of the murmur and clinical improvement, was 60%. There was no difference in gestational age and postnatal age at treatment between infants in whom the PDA was closed with treatment and those who did not close their PDA. There were no differences in gestational ages, birthweights, duration of treatment with oxygen, presence of IVH, aROP, or cROP between groups (Table). The occurrence of HMD and the use of exchange transfusions were significantly higher in group 1 than group 2.

Discussion

PDA is a very common problem in preterm infants especially those ≤ 1500 g. Oxygen is thought to be an important factor determining constriction of the ductus arteriosus⁹ and group E prostaglandins seem to have an important role in keeping the ductus patent in the newborn period.¹⁰ Indomethacin, a prostaglandin synthetase inhibitor, has been used for closure of PDA in preterm infants.¹¹⁻¹² The effect of the different groups of prostaglandins as well as of indomethacin on the retinal vessels is not known. However, it is well established that the retinal circulation responds to high oxygen concentration with vasoconstriction.⁴ Any factor determining retinal vasoconstriction is potentially a cause of ROP,⁴ and the effects of PDA treatment with prostaglandin synthetase inhibitor on the retinal vessels remain to be determined.

Some aspects of our study deserve comment. This was a retrospective study, therefore a randomised study was not possible. However, birthweights, gestational ages, duration of treatment with oxygen, and occurrence of IVH, aROP, or cROP were not different when we compared both groups. We did not attempt to correlate the incidence of ROP with intermittent determinations of Pao_2 , as in previous studies it had not been possible to do so.¹³ The introduction of transcutaneous Pao_2 monitoring will permit such studies. We did not take into consideration the influence of simple blood transfusions on the occurrence of ROP, because most of the patients required blood in the first month of life. However, the use of exchange transfusion was higher in the treated group. It has been questioned whether this procedure might potentiate the risk for ROP in preterm infants.¹⁴⁻¹⁵

The occurrence of IVH in treated and untreated groups was the same. All intraventricular haemorrhages occurred before the use of indomethacin (mean 11.3 days) and no clinical symptoms of IVH were noted after treatment; however, CAT scans were not performed after treatment with indomethacin.

Our data suggest that the use of indomethacin for closure of symptomatic PDA in preterm infants does not increase the incidence of ROP. However, our numbers are small and large prospective studies should be performed. Careful consideration should be given before using indomethacin for closure of the PDA.

These studies were supported in part by a grant from the Retina Research Foundation, Houston, Texas.

References

- ¹ Heymann M A, Rudolph A M, Silverman N H. Closure of the ductus arteriosus in premature infants by inhibition of prostaglandin synthesis. *N Engl J Med* 1976; **295**: 530-3.
- ² Friedman W F, Hirschklau M J, Printz M P, Pitlick P T, Kirkpatrick S E. Pharmacologic closure of patent ductus arteriosus in the premature infant. *N Engl J Med* 1976; **295**: 526-9.
- ³ Schrage G O. Letter: PDAs, prostaglandins, and RLF. *Pediatrics* 1978; **62**: 860-1.
- ⁴ James L S, Lanman J T. History of oxygen therapy and retrolental fibroplasia. *Pediatrics* 1976; **57**: Supplement, 591-642.
- ⁵ Battaglia F C, Lubchenco L O. A practical classification of newborn infants by weight and gestational age. *J Pediatr* 1967; **71**: 159-63.
- ⁶ Dubowitz L M, Dubowitz V, Goldberg C. Clinical assessment of gestational age in the newborn infant. *J Pediatr* 1970; **77**: 1-10.
- ⁷ McCormick A Q. Retinopathy of prematurity. In: Gluck L, ed. *Current problems in pediatrics*, vol. 7, No. 11. Chicago: Year Book Medical Publishers, 1977: 1-28.
- ⁸ Reese A B, King M J, Owens W C. A classification of retrolental fibroplasia. *Am J Ophthalmol* 1953; **36**: 1333-7.
- ⁹ Rudolph A M. The ductus arteriosus and persistent patency of the ductus arteriosus. In: Rudolph A M, ed. *Congenital diseases of the heart*. Chicago: Year Book Medical Publishers, 1974: 168-201.
- ¹⁰ Friedman Z, Demers L M. Essential fatty acids, prostaglandins, and respiratory distress syndrome of the newborn. *Pediatrics* 1978; **61**: 341-7.
- ¹¹ Heymann M A. Management of PDA with prostaglandin synthetase inhibitors. In: Heymann M A, Rudolph A M, eds. *The ductus arteriosus. Report of the seventy-fifth Ross conference on pediatric research*. Columbus, Ohio: Ross Laboratories, 1978: 84-6.
- ¹² Friedman W F, Fitzpatrick K M, Merritt T A, Feldman B H. The patent ductus arteriosus. *Clin Perinatol* 1978; **5**: 411-36.
- ¹³ Kinsey V E, Arnold H J, Kalina R E, et al. PaO₂ levels and retrolental fibroplasia. A report of the cooperative study. *Pediatrics* 1977; **60**: 655-68.
- ¹⁴ Bard H, Cornet A, Orguin J, Doray B H. Retrolental fibroplasia and exchange transfusions (abstract). *Pediatr Res* 1975; **9**: 362.
- ¹⁵ Lechner D, Kalina R E, Hodson W A. Retrolental fibroplasia and factors influencing oxygen transport. *Pediatrics* 1977; **59**: 916-8.

Correspondence to Dr Joseph A Garcia-Prats, Department of Pediatrics, Baylor College of Medicine, Texas Medical Center, Houston, Texas 77030, USA.

Received 8 May 1979