Is oral indomethacin effective in treatment of preterm infants with patent ductus arteriosus?

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SUMMARY: Satar M. Yapıcıoğlu H, Narlı N, Özbarlas N, Küçükosmanoğlu O, Tutak E. Is oral indomethacin effective in treatment of preterm infants with patent ductus arteriosus? Turk J Pediatr 2004; 46: 137-141.

Twenty-one preterm infants (with a mean gestational age and birth weight of 29.3 weeks and 1288.6 g) and nine pretem infants (with a mean gestational age and birth weight of 29.6 weeks and 1153.1 g) were treated with an enteral preparation of indomethacin and with intravenous indomethacin, respectively, for the closure of hemodynamically significant ductus arteriosus. The patients received three doses of either oral indomethacin capsule (Endol, Deva, Turkey) or intravenous indomethacin (Confortid, Dumex GmBH, Germany) in a dose of 0.2 mg/kg at 12-hour intervals. The ductus was closed in 17 (81%) and 7 (77%) of the babies in the orally and intravenously treated groups, respectively ($p>0.05$). There was no significant difference in blood urea nitrogen, creatinine levels or thrombocyte counts in either group before and after treatment with indomethacin ($p>0.05$). No side effect was reported in the oral indomethacin group. Oral indomethacin may be an alternative to the intravenous preparation in developing countries if the intravenous form is not available or not affordable.

Key words: patent ductus arteriosus, oral indomethacin.

During fetal life most of the pulmonary arterial blood is shunted through the ductus arteriosus into the aorta. Functional closure of the ductus normally occurs soon after birth. If the ductus remains persistant, aortic blood is shunted to the pulmonary artery. It is a common problem in premature infants and causes hemodynamic derangements and several major sequelae[1]. In term infants it is mostly because of the deficiency of both the mucoid endothelial layer and muscular media of the ductus. In contrast, patency of prematurity is the result of hypoxia and immaturity[1].

Intravenous indomethacin has been used in the treatment of patent ductus arteriosus (PDA) and found to be effective[2-6]. But, in some developing countries, it is still difficult to obtain the intravenous form and it is expensive. We have been using oral indomethacin for the closure of PDA since 1993 if the intravenous form cannot be acquired. This retrospective study of 30 neonates with echocardiographic evidence of PDA was conducted to identify the effectiveness and side effects of oral indomethacin therapy compared with the intravenous form.

Material and Methods

Neonates with PDA treated with oral and intravenous indomethacin in the Neonatal Intensive Care Unit (NICU), Çukurova University Faculty of Medicine, between January 1994 and October 2002 were enrolled in the study group. We have been using oral indomethacin for the closure of PDA since 1993 if the intravenous form is not available. Infants with complex cardiac anomalies and congenital anomalies were not included. Data pertaining to maternal history, antepartum events, gestational age, birth weight, gender, Apgar scores, presence of meconium in amniotic fluid, use of antenatal betamethasone, need and dose of surfactant and indomethacin, echocardiographic findings, cranial ultrasonographic (USG) findings, thrombocyte count, blood urea nitrogen (BU),

serum creatinine values and outcome of patients were collected retrospectively. The values are given as mean ±SD (min-max) in the text.

The ductus arteriosus was evaluated from suprasternal and high parasternal views by two-dimensional echocardiography with pulsed, continuous wave and Doppler measurements using 5 and 7 mHz transducers (General Electrics 6800) and repeated after treatment by the same pediatric cardiologists. Cranial USG was recorded by the same radiologist, and intraventricular hemorrhage (IVH) was graded as suggested by Papile et al.[7].

Infants were treated with three separate 0.2 mg/kg doses of either oral intravenous indomethacin at 12-hour intervals if there were no contraindications (BUN >40 mg/dl, serum creatinine concentration >1.8 mg/dl, urine output <0.6 ml/kg/hr, thrombocytopenia <40000/mm^3, active bleeding, necrotizing enterocolitis (NEC) or coagulation defects). NEC was diagnosed according to the criteria of Walsh and Kligman[8]. Content of indomethacin capsule (Endol, Deva, Turkey) was diluted in 10 ml 0.9% normal saline, and intravenous indomethacin (Confortid, Dumex GmBH, Germany) was diluted in 10 ml distilled water. If PDA was not closed, treatment was repeated with the same dose. Bronchopulmonary dysplasia has been defined as a need for supplemental oxygen and evidence of an abnormal chest X-ray at more than 28 days of life and oxygen dependence beyond 36 weeks postconceptionally[9,10].

Blood urea nitrogen (BUN), serum creatinine concentration, electrolytes, and thrombocyte count were measured before and after indomethacin treatment. Patients were weighed daily. Premature newborn infants were usually given 60 ml/kg/d and term babies were given 80 ml/kg/d on the first day of life, after which fluid intake of subjects was adjusted according to urine density and weight changes. Their files in neonatology and pediatric cardiology outpatient clinics were examined and it was noted if reopening of ductus occurred.

Statistical Analysis: Statistics were analyzed using the SPSS-X 9.0 for Windows. Chi-square and t tests were used for independent samples and, when necessary, Mann-Whitney U tests were performed.

Results

Thirty preterm infants with a mean gestational age of 29.4±1.9 (27-35) weeks and a mean birth weight of 1247.9±203 (850-1650) g were enrolled in the study. Nineteen (63.3%) were female. Three of the mothers had preeclampsia, one had eclampsia, four had prolonged rupture of membranes and one had antenatal betamethasone. In two subjects atrial septal defect was present and three subjects had small ventricular septal defect causing no significant hemodynamic derangement. None had pulmonary hypertension. Thirteen (43.3%) had respiratory distress syndrome and eight (26.6%) of them were treated with surfactant. The characteristics of the patients are given in

Table I. Characteristics of 30 Patients Treated with Oral and Intravenous Indomethacin for Patent Ductus Arteriosus (PDA)

		Oral (n:21)	Intravenous (n:9)	p
Gender (n, %)	female	15 (71.4)	4 (44.4)	>0.05
	male	6 (28.6)	5 (55.6)	>0.05
Gestational age (weeks)		29.3±1.9 (27-35)	29.6±1.9 (28-33)	>0.05
Birth weight (g)		1288.6±208.5 (900-1650)	1153.1±162.3 (850-1390)	>0.05
PDA diagnosis age (days)		7.2±3.7 (1-15)	10.78±6.1 (3-19)	<0.05
Indomethacin course	once	18	8	>0.05
	twice	3	1	
Ductus closure rate (n, %)		17 (81)	7 (77.8)	>0.05
Duration of hospitalization (days)		27.9±20.3 (5-69)	42.2±12.9 (19-59)	>0.05

Table I. In the oral indomethacin group there were 21 (15 female, 6 male) preterm infants and in the intravenous group there were 9 (4 female, 5 male) preterm infants. The mean gestational age and birth weight of the oral and intravenous groups were 29.3±1.9 (27-35) weeks, 1288.6±208.5 (900-1650) g and 29.6±1.9 (28-33) weeks, 1153.1±162.3 (850-1390) g, respectively ($p>0.05$). PDA was diagnosed on the 7.2±3.7 (1-15) days of life in the oral group and on the 10.78±6.1 (3-19) days of life in the intravenous indomethacin group ($p<0.05$). Three patients in the oral and one patient in the intravenous group had two courses of indomethacin ($p>0.05$). PDA was 2.5 mm in two patients in the intravenous group and in one patient in the oral group; in one of the two objects in the intravenous group PDA did not close after treatment. The other patients had PDA of less than 2 mm.

All subjects were fluid restricted. One in the intravenous indomethacin group needed digoxin; four (3 in the oral group) needed furosemide ($p>0.05$). There were no statistically significant differences in mean BUN, serum creatinine values and thrombocyte counts within/between groups before and after oral indomethacin treatment ($p>0.05$) (Table II). Urine output after treatment was 2.2±1.3 (0.9-4.1) ml/kg/hr. There was no gastrointestinal system bleeding, but two infants in the intravenous indomethacin group developed NEC. Three babies (1 in oral indomethacin group and 2 in intravenous indomethacin group) had bronchopulmonary dysplasia ($p>0.05$). Cranial USG could not be performed routinely because there was no ultrasonography in the NICU before 1999. Cranial USG was performed on 18 patients. Three of nine patients (2 Grade II, 1 Grade III) and four of nine patients (2 Grade II, 2 Grade III) had intraventricular hemorrhage (IVH) in the oral and intravenous groups, respectively. There was no expansion in the hemorrhage area after treatment in either group. PDA was closed in 81% and 77.8% of patients in the oral indomethacin group and intravenous indomethacin group, respectively ($p>0.05$). None of the patients needed surgical ductus ligation. There were no statistically significant differences between groups in mean gestational age, birth weight, diseases of mother, rate of respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD), use of betamethasone, ventilator treatment, indomethacin course, ductus closure, duration of hospitalization or mortality rate ($p>0.05$). There was no reopening of PDA.

Discussion

Patent ductus arteriosus is a challenging problem to neonatologists and cardiologists. In a large network of neonatal intensive care units, the frequency of PDA in infants weighing 501 to 1500 g was 31%[11]. Substantial left to right shunting through the ductus may increase the risk of IVH, NEC, BPD and death[12,13]. Conventional medical treatment of PDA includes fluid restriction and congestive cardiac failure treatment, followed by indomethacin. Successful pharmacological closure of PDA with indomethacin was first reported in 1976[2,3] and has been found to be effective, with a reported efficacy of 70%-80% in various studies[2,4-6]. Indomethacin has been shown to be effective in closing the ductus and reducing complications such as NEC, retinopathy of prematurity (ROP), BPD, and IVH related to PDA[6,13].

Three doses of intravenous 0.2 mg/kg lyophilized indomethacin are recommended. There are studies reporting the oral use of indomethacin[14-16]. So et al.[14] treated 41 infants with a mean gestational age and birth weight of 29.7 weeks and 1322 g, respectively, with oral indomethacin. The ductus arteriosus was closed in 71% of the patients. Shanthala et al.[15] used

Table II. BUN, Serum Creatinine and Thrombocyte Count of 30 Patients with Patent Ductus Arteriosus Before and After Treatment

	Before treatment	After treatment	p
BUN (mg/dl)	22.5±19.2 (8-114)	21.8±13.4 (5-52)	>0.05
Serum creatinine (mg/dl)	0.95±0.5 (0.5-3.1)	0.93±0.4 (0.5-2.2)	>0.05
Thrombocyte count (/mm^3)	176.500±84.000 (44.000-408.000)	146.600±72.800 (60.000-352.000)	>0.05

BUN: Blood urea nitrogen.

three doses of 0.2-0.25 mg/kg/dose oral indomethacin in 16 neonates along with fluid restriction and oxygen, and 81.3% of infants responded to treatment. In our study 81% of the subjects responded to therapy in the oral indomethacin group and closure rate was not significantly different from that of the intravenous indomethacin group.

Indomethacin has some side effects on cerebral and gastrointestinal systems and on renal perfusion causing NEC or isolated bowel perforation, oliguria and transient renal failure[13,17-20]. We did not observe a significant side effect. There was no statistically significant difference between BUN, creatinine and thrombocyte values before and after indomethacin treatment in/between groups. So et al.[14] reported two ileal perforations in their patients treated with oral indomethacin (5%), but we did not find NEC in the oral indomethacin group. Although NEC seems to be statistically significantly higher in the intravenous group, we think it is a complication of PDA and prematurity rather than a complication of intravenous indomethacin.

In the study by Maher et al.[21] they suggested oral indomethacin therapy did not cause an expansion of a preexisting intracranial bleeding. Ment et al.[22] showed low-dose indomethacin significantly lowered the incidence and severity of IVH. Davis et al.[23] reported that intravenous indomethacin did not worsen IVH. We detected no increase in IVH after treatment.

Reopening may occur after indomethacin treatment and it is more frequent in infants treated after the first week compared with those who received indomethacin in the first two days[24]. Weiss et al.[25] reported reopening in 21% of 77 patients, with significance in preterms. We did not report a reopening.

In conclusion, we saw no significant side effect related to the oral form of indomethacin, and ductus closure was similar to that observed in the intravenous indomethacin treatment. As the outcome of treatment with this enteral preparation of indomethacin is comparable with that of intravenous preparation, it may be an alternative to the intravenous preparation in areas where the intravenous form is not available or affordable. Further studies including a large number of patients may extend the use of oral indomethacin.

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