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Oral Ibuprofen for Closure of Hemodynamically Significant Patent Dultus Arteriosus in Premature Neonates: a Pilot Study

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Abstract

Background- A patent ductus arteriosus (PDA), resulting in hemodynamically-significant left to right shunting of blood, increases complications and mortality in premature infants. PDA in premature infants is conventionally treated by intravenous indomethacin. Intravenous ibuprofen was recently shown to be as effective, but to have adverse reactions in premature infants. If equally effective, then oral ibuprofen for PDA closure would have several important advantages over the intravenous route. This study was designed to determine whether oral ibuprofen treatment is efficacious and safe in the closure of a hemodynamically-significant PDA in premature infants.

Methods- Ten premature infants with symptomatic PDA were studied prospectively. The average gestational age and weight of them were 29.5 weeks and 1320 g, respectively. The neonates were diagnosed to have symptomatic PDA based on the clinical criteria, chest radiography and echocardiography. All the babies had CBC, PT, BUN, serum electrolytes and U/A done before and after therapy. They received oral ibuprofen for three consecutive daily doses. All the neonates underwent repeat echocardiography 24 h after three doses of ibuprofen.

Results- Ductus closure was achieved in all the newborns except for one (90%). There were no significant side effects like oliguria or bleeding tendencies. There was no reopening of the ductus after the closure had been achieved.

Conclusion- Ibuprofen, unlike indomethacin, dose not impair cerebral autoregulation and has much fewer adverse effects on the renal and mesenteric circulation. Oral ibuprofen suspension may be an effective and safe alternative for PDA closure in premature infants with PDA. However, larger comparative studies are warranted ***(Iranian Heart Journal 2006; 7 (2):15-18)***.

Key words: Premature neonates ▪ Ibuprofen ▪ patent ductus arteriosus

The ductus arteriosus, a large channel normally found in all mammalian fetuses, develops from the distal portion of the left sixth aortic arch and connects pulmonary artery at its bifurcation to the descending aorta just distal to the origin of the left subclavian artery.

arteriosus differs from that of the adjacent pulmonary trunk or aorta.[1]
During fetal life, the patency of the ductus arteriosus appears to be maintained by the combined relaxant effects of low oxygen tension and endogenously produced

specifically prostaglandin E2.

The effects of oxygen on the ductal smooth muscle may be direct or mediated by its effects on prostaglandin synthesis.[2,3]

It closes after birth first functionally and then anatomically; but if remained open, it causes L→R shunt. There are usually no symptoms associated with a small patent ductus. A large PDA will result in heart failure similar to that encountered in infants with a large VSD.

Methods

We evaluated 10 premature neonates with symptomatic PDA prospectively. The neonates were diagnosed to have symptomatic PDA based on the following criteria: (1) systolic or continuous murmur (Grade II or more) in left infraclavicular region; (2) presence of at least three of the following: (a) basal tachycardia (heart rate>170/min), (b) bounding brachial and femoral arterial pulses, (c) hyperdynamic left ventricular impulse, (d) tachypnea (respiratory rate>70/min), and (e) other evidence of cardiac failure, e.g., tender palpable liver>3 cm below the costal margin and crepitations on chest auscultation; (3) cardiomegaly (cardiothoracic ratio>0.6) with pulmonary plethora on chest radiograph; and (4) echocardiography. All the babies had a complete blood count, platelet count, prothrombin time, blood urea nitrogen (BUN), serum electrolytes and creatinine and urine examination done before and after therapy. Babies with major congenital anomalies, complex heart disease, evidence of a bleeding diathesis, platelet count<60,000/mm³, clinical or radiographic evidence of NEC, urine output <0.6 ml/kg/h, BUN> 30 mg/dl, and serum creatinine>1.8 mg/dl were excluded from the study. The babies received oral ibuprofen 10 mg/kg for the first dose, followed by 5 mg/kg at 24 and 48 hours after the start of treatment. All the neonates underwent repeat echocardiography to confirm closure of PDA 24 h after three doses of ibuprofen.

Results

Ten premature infants with symptomatic PDA were treated with oral ibuprofen .The average gestational age and weight of them were 29.5 weeks (range: 24-36 weeks) and 1320 g (range: 970-1900 g), respectively. Table I summarizes the outcome of these 10 neonates. Ductus closure was achieved in all the newborns except for one (90%) after treatment. There were no significant side effects like oliguria or bleeding tendencies after treatment with oral ibuprofen. There was no reopening of the ductus after closure had been achieved.

Table 1. Summary of the outcome of 10 neonates with symptomatic PDA treated with oral Ibuprofen

Gestation (weeks)	Diagnosis	Weight (Kg)	Age at ibuprofen therapy (day)	Outcome
26	AGA with HMD	1.05	7	Success
24	AGA with RDS	1.22	11	Success
26	AGA with HMD	1.25	7	Success
36	AGA with HMD	1.9	9	Success
33	SGA with RDS	1.37	6	Failure
26	AGA with HMD	0.97	11	Success
32	SGA with RDS	1.2	11	Success
29	AGA with HMD	1.32	9	Success
32	AGA with RDS	1.5	11	Success
29	AGA with RDS	1.32	9	Success

Discussion

The advance of medical science and improvement of premature infant care have increased the survival of infants. Premature infants, defined as gestational age of less than 37 weeks, are at greater risk and complications compared with term infants. For example, the risk of sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus is high in these infants. [4]

The incidence of isolated PDA in full-term

infants is about 1 in 2,000 live births, accounting for about 5% to 10% of all types of congenital heart disease.[5] Because the constrictor response of the ductus arteriosus to oxygen and the dilator effect of PGE2 are closely related to gestational age, it is not surprising that there is an extremely high incidence of PDA in low-birth-weight preterm infants, particularly very low-birth-weight infants (less than 1,ooo g) and those with pulmonary disease. Overall, the incidence of PDA in preterm infants is about 8 per 1,000 of live births. As with all left-to-right shunts, with PDA three major, interrelated factors control the magnitude of shunting: the diameter and length of the ductus arteriosus; the pressure difference between the aorta and the pulmonary artery; and the systemic and pulmonary vascular resistances.

The clinical features depend on the magnitude of the left-to-right shunt through the PDA and the ability of the infant to initiate compensatory mechanisms to handle the extra volume load. Because many premature infants have respiratory distress syndrome, the stage of development of this disease and the use of surfactant replacement therapy will determine the pulmonary vascular resistance and therefore the shunt. The maturity of the infant and the stage of myocardial development determine the ability to handle the shunt.[1]

As previously noted, PDA is a common finding among premature infants. Hemodynamically-significant PDA may complicate the clinical outcome of preterm infants. A PDA is associated with an increased risk of intraventricular hemorrhage, necrotizing enterocolitis, chronic lung disease, and death.[6] Historically, progress in the management of the preterm infant with a PDA includes surgical closure, introduced in the early 1970s by Kitterman et al.[7], and the use of i.v. indomethacin introduced by Heyman et al.[8] and Friedman et al.[9] in the mid-1970s. Indomethacin inhibits the two isoforms of the enzyme cyclooxygenase to varying degrees, leading to a reduced synthesis of prostaglandins. Intravenous indomethacin has been widely used for ductal closure in premature infants.[8,10,11] Indomethacin may affect the renal, cerebral and gastrointestinal systems leading to NEC, decrease in intracerebral oxygenation, or gastrointestinal hemorrhage.[12,13] Ibuprofen like indomethacin belongs to the group of non steroidal anti-inflammatory drugs that prevent the conversion of arachidonic acid to PGE2 thus preventing patency of PDA. In the last few years, much evidence has emerged regarding the safety and efficacy of ibuprofen for the treatment of preterm PDA. Intravenous ibuprofen was recently shown to be as effective, but to have adverse reactions in premature infants.[14] Ibuprofen dose not impair cerebral autoregulation and has much fewer adverse effects on the renal and mesenteric circulation.[15,16,17,18] A recent study conducted in a large number of preterm infants suggests that ibuprofen should be preferred as the first line of drug for closing PDA in preterm infants.[14]

In conclusion, in our limited experience we found oral ibuprofen a safe and effective drug for the closure of hemodynamically-significant PDA in preterm infants. Larger randomized controlled trials for comparison with other drugs like indomethacin and mefenamic acid are warranted.

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