Oral Ibuprofen Therapy for Patent Ductus Arteriosus in Very Low Birth Weight Infants

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Abstract

Background- Patent ductus arteriosus is found in 45% of infants under 1500gr and in infants weighing < 1000gr, the incidence is closer to 80%. Indomethacin has been shown to close the ductus arteriosus in a large fraction of premature infants. Intravenous ibuprofen was recently shown to be as effective and to have fewer adverse reactions in preterm infants. If equally effective, then oral ibuprofen for patent ductus arteriosus (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 closure of PDA in very low birth weight infants with respiratory distress syndrome (RDS).

Methods- 30 preterm newborns (gestational age 28.3±2.6 weeks), mean weight 1130±312gm, with PDA and RDS were studied prospectively. They received oral ibuprofen suspension 10mg/kg/body weight for the first dose, followed at 24 hour intervals by two additional doses of 5mg/kg each, if needed, starting on the second day of life. Echocardiographies were performed before treatment and 24 hours after the second dose. The rate of ductal closure, the need for additional treatment, side effects, complications and the infants' clinical courses were recorded.

Results- Ductal closure was achieved in 28 newborns (93.3%), and in two others partial closure was achieved with no important shunts persisting. No infants required surgical ligation of ducts. There was no reopening of the ductus after closure had been achieved. 21 newborns were treated with one dose of ibuprofen, five were treated with two doses and the remaining two were treated with three doses. There were no significant differences in the levels of serum creatinine before and after treatment with oral ibuprofen.

Conclusion- 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 2008; 9 (2):23-28).***

Key words: ibuprofen ■ very low birth weight ■ patent ductus arteriosus

The incidence of PDA is inversely related to gestational age. PDA is found in 45% of infants under 1500g, and in infants weighing<1000g, the incidence is closer to 80%. The initial presentation may be at birth, but is usually at days 1-4 of life.[1]

Closure is often warranted in VLBW infants with RDS, as significant left-to-right shunting through the ductus may increase the risk of intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia, and death.[2,3,4]

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Pharmacologic closure of the ductus arteriosus in premature infants with symptomatic left-to-right shunting has been shown to decrease morbidity.[5] Indomethacin is a prostaglandin synthesis inhibitor that has proved to be effective in promoting ductal closure. Its effectiveness is limited to VLBW infants and also decreases with increasing postnatal age. Thus it will have limited efficacy beyond 3-4 weeks of age, even in VLBW infants. Indomethacin has been used widely in the prophylaxis and treatment of hemodynamically significant PDA.[6,7] Treatment with indomethacin, however, may be associated with adverse reaction, such as decrease renal flow and GFR, gastrointestinal bleeding, platelet dysfunction, and increased IVH.[8-14] Ibuprofen, another prostaglandin synthesis inhibitor, has been shown to be as effective as indomethacin for ductal closure by several investigators who administered it intravenously.[15-17] In contrast to indomethacin, ibuprofen dose not affect basal cerebral blood flow or intestinal or renal hemodynamics.[16-22] If it could be shown to be as efficacious and as safe as the intravenous route, then oral ibuprofen would afford several important advantages:

1) Intravenous indomethacin and ibuprofen is not available in Iran or in many other countries.
2) The required oral dose is of minimal volume (0.25-0.5 ml for infants who weigh 500-1000g).
3) Oral administration is extremely simple
4) The oral form of drug is less expensive than the intravenous.

This study was designed to determine whether oral ibuprofen treatment is efficacious and safe in closure of a PDA in very low birth weight infants with RDS.

Methods

30 very low birth weight premature newborns who were treated at our department between Jan. 2004 and April 2006 were recruited prospectively.

Neonates who were admitted to the study were enrolled when the following criteria were met: 1) gestational age < 32 weeks; 2) weight < 1500g; 3) postnatal age 45-96 hours; 4) RDS on chest radiograph necessitating treatment with survanta, mechanical ventilation and need for oxygen supplementation above 25%; 5) echocardiographic evidence of hemodynamically significant PDA (left atrium/aortic root diameter ratio>1.4 or ductal size>1.5mm). Color Doppler showed continuous flow, Doppler echo showed max. pressure gradient 40-60 mmHg. Exclusion criteria were: 1) major congenital anomalies; 2) IVH of grade III; 3) serum creatinine > 1.5mg/dL, 4) serum urea nitrogen concentration >50mg/dL; 5) Platelet count <60.000/mL^3 and 6) tendency to bleeding.

All infants that met the entry criteria first underwent echocardiography, after which they were treated with ibuprofen 10mg/kg administered through a feeding tube. The imaging procedures were performed 24 hours after two doses. When the PDA was still hemodynamically significant, as deterioration by echocardiography showed, a second dose of ibuprofen 5mg/kg was administered. A third equivalent dose was given after another 24 hours if deemed necessary. Treatment of PDA in preterm infants with RDS is indicated before a significant left-to-right shunting occurs. Birth weight, gestational age and clinical outcomes were recorded prospectively.

Color Doppler echocardiography (Sonosite Echo with 2-5 MHz probe, 2-D, Doppler and color Doppler) was performed on all infants who were clinically suspected of having PDA. This was conducted by a pediatric cardiologist who was blind to the treatment being given. Patients with clinical signs of PDA such as tachycardia (>160 beats/min), presence of a murmur, and bounding pulses were eligible for the study and underwent an echocardiographic evaluation before entry to

the study. PDA was considered echocardiographically significant when the ductal size was >1.5mm or the left atrial-to-aortic root ratio was >1.4.

Results

A total 102 premature infants at gestational age <32 weeks and birth weight <1500g were admitted during the study period. 30 of them were eligible for entry in the study and underwent an echocardiographic Doppler ultrasound evaluation at age 48 to 72 hours.
The baseline characteristics of the 30 very low birth weight and premature infants are presented in Table I.

Table I. Baseline characteristics of the study infants

Birth weight (g)	**1130±312 (range 600-1500)**
Gestational age (wk)	28.3±2.6 (range 28-31)
Surfactant treatment	30
IVH G I G II G III	 16.6 6% 26%
Ductal diameter (mm)	2.4±0.83 (range 1.5-3.7)
Degree of ductal shunting	
Mod	22 (73.3%)
Sever	6 (20%)

The rate of PDA closure was 93.3% (28 of 30 cases). There was reopening of PDA after closure. No infant required surgical ligation of the ductus (Table II).

Table II. Efficacy of treatment by ibuprofen

Age at start of treatment (d)	2.3±0.4 (range 2-4)
No. of closed PDA	28 (93.3%)
No. of ibuprofen doses	1.47±0.7 (range 1-3)
Surgical ligation	0

21 newborns were treated with one dose of ibuprofen, five were treated with two doses and the remaining two were treated with three doses. The survival rate at 1 month was 100% (Table III).

Table III. Outcome of the study infants (n=30)

Death	0
NEC	2
Sepsis	5
IVH	9

There were no significant differences in the levels of serum creatinine before and after treatment with oral ibuprofen (P=0.37; Table IV).

Table IV. Changes in serum creatinine (mg/dl)

Day 1 (24 hrs after ibuprofen administration)	0.86±0.12 (range 0.6-1.4)
Day 2 (48 hrs after ibuprofen administration)	0.86±0.12 (range 0.7-1.4)
Day 3 (72 hrs after ibuprofen administration)	0.82±0.11 (range 0.6-1.2)
Pretreatment increase in creatinine 1 to 3	P=0.37
Comparison of creatinine between 1 and 2	P=0.46
Comparison of creatinine between 2 and 3	P=0.39

Discussion

Intravenous ibuprofen has been shown to be as effective as indomethcin in PDA closure.[15-17] If treatment with oral ibuprofen is both effective and safe, then it would have the advantages of more widespread availability, simpler administration and decreased cost. The primary objective of the current study was to determine whether orally administered ibuprofen treatment is effective in PDA closure in VLBW and preterm infants with RDS. Our results showed oral ibuprofen to be effective and safe in PDA closure with 28 of 30 (93.3%) study infants achieving a successful outcome. This frequency of closure is significantly higher then the figure of 70% reported by Van Overmeire's group[17] (P=0.015) where ibuprofen was higher compared with the other studies in which indomethacin success is reported at 71 to 77%.[3,23] Because ductal closure was achieved most of our infants and in two patients the residual defect was not clinically significant, there was no need for rescue therapy or surgery. The pharmacokinetics of oral ibuprofen among preterm infants and infants older than 3 months have been studied and reported.[24-27] The findings indicate that ibuprofen is absorbed rapidly after oral administration, and peak concentrations in plasma are observed after 1 to 2 hours. Among infants older than 3 months, the age of the child does not significantly influence the rate of absorption of ibuprofen, the plasma concentration of the drug, or its rate of elimination. With oral administration of ibuprofen, a small inter-individual variability in the pharmacokinetics of the drug is observed.[24,25] It is possible though, that the slower rate of oral ibuprofen absorption, together with the longer time to peak plasma level as compared with the intravenous route, and the prolonged time of contact and exposure of the ductus to ibuprofen, enables ibuprofen to exert its pharmacologic effect longer and with greater effect then the intravenous route. In the study by Raju et al,[27] in which ibuprofen was administered orally or intravenously to nine preterm infants for the prevention of bronchopulmonary dysplasia, the study drug was withdrawn in one infant after 8 days (15 doses) of treatment because of gastrointestinal hemorrhage that occurred 6 hours after the last dose. However, this infant also received steroids and aminophylline, which potentially can cause gastrointestinal bleeding, and it is not clear whether this infant received intravenous or oral ibuprofen.[27] Furthermore, adverse gastrointestinal reactions have been observed among preterm and term infants whose mothers were treated with antenatal indomethacin without direct contact of the nonsteroidal anti-inflammatory drugs with the gastrointestinal tract of the newborn.[28-32]

Serum creatinine levels in our patients were within normal range at all times, so there was no contraindication for a second or third dose of ibuprofen when it was needed. This might be an explanation for the higher rate of pharmacologic ductal closure observed in our study. There are several limitations to our study. This was an open-label, one-arm study and the there was no matched control group. IVH was observed in nine infants (Table1). IVH is a common complication during the first days of life in premature infants, and its presence or extension therefore might be the natural history of IVH or a complication of PDA in premature infants, and not necessarily related to ibuprofen treatment. Gournay et al.[33] described three cases of severe hypoxemia after intravenous ibuprofen administration during prophylactic treatment of PDA in premature infants who were born at <28 weeks of gestation within the first six hours after birth, which is earlier than that reported in most previous studies. Their three infants had been stable before the prophylactic drug was given and developed refractory hypoxemia within one hour after receiving the first dose. Echocardiographic examinations showed severely decreased pulmonary blood flow in all three cases. No incidents of severe

hypoxemia or decreased pulmonary blood flow on echocardiographic examination after administration of the drug occurred among our study patients.

The physicians and nurses were aware of the nature of the study, although the cardiologist who supervised the echocardiographic studies was blind to the status of the infants and whether or not they were treated with oral ibuprofen. Intravenous ibuprofen has 100% bioavailability: the bioavailability of the oral ibuprofen administered in our study was not measured.

Conclusion

The results of our study on a small-sized population indicate that oral ibuprofen may be an effective and safe alternative to intravenous ibuprofen for PDA closure in VLBW and premature infants. Larger comparative studies are needed to validate these findings.

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