

Early and late outcome of treatment with oral ibuprofen in preterm infants suffering from patent ductus arteriosus: A randomized clinical trial

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Abstract

Background and Objective: Nonsteroidal anti-inflammatory agents are the treatment of choice for ductal closure in premature newborn. This study evaluates early and late outcome, as well as the effectiveness of oral ibuprofen in the treatment of patent ductus arteriosus (PDA) in premature infants.

Methods: In this clinical trial, all preterm infants below 37 weeks, with documentation of PDA were enrolled. Infants were divided into two groups. The case group (19 patients) was treated with three doses of oral ibuprofen. Control group (19 patients) were under restriction of fluids (serum level of $\frac{2}{3}$ maintenance). The rate of ductal closure, presence of pulmonary hypertension were determined at the age of one week, one month, 3 months and 6 months and intraventricular hemorrhage and periventricular leukomalacia (PVL) were detected at the age of one week and one month. The presence of retinopathy was checked at the time of hospital discharge and at the age of one month.

Results: Ductal closure was achieved in all newborn of the ibuprofen group whereas in control group ductal closure rate was 16.19 (84.2%) ($p=0.23$). No case of pulmonary hypertension, PVL or retinopathy was observed in oral ibuprofen group. Regarding to other criteria such as hospital stay, intraventricular hemorrhage, sepsis, ventilator time dependence, pulmonary hemorrhage and mortality rate, no significant difference between the two groups was observed.

Conclusions: Oral ibuprofen suspension may be an effective and safe alternative for PDA closure in premature infants. However larger studies are warranted.

Keywords: Oral ibuprofen, Patent ductus arteriosus, Premature infants

Introduction

A patent ductus arteriosus (PDA) complicates the clinical course of preterm infants, increasing their risks of developing chronic lung disease (CLD), necrotizing enterocolitis (NEC), and causes intraventricular hemorrhage (IVH) (1,2). Pharmacologic closure of the ductus arteriosus in premature infants with symptomatic left to right shunting has been shown to decrease morbidity (3,4).

Indomethacin, a prostaglandin synthesis inhibitor, has been used widely in the prophylaxis and treatment of hemodynamically significant PDA.

Treatment with indomethacin, however, may be associated with adverse reactions, such as reduced renal, mesenteric, and cerebral perfusion. Decreased perfusion of these vascular beds may lead to renal dysfunction, NEC, gastrointestinal hemorrhage, and IVH or periventricular leukomalacia (5).

Ibuprofen, another cyclooxygenase inhibitor, may be as effective as indomethacin, with fewer side effects (3,6,7). In contrast to indomethacin, ibuprofen does not affect basal cerebral blood flow, cerebral metabolic rate, or interstitial or renal hemodynamics (8). If it could be effective and

safe as intravenous indomethacin, then oral ibuprofen would afford several important advantages: 1) intravenous ibuprofen is not available in Iran or in many other countries, 2) oral administration is extremely simple, and 3) the oral form of the drug is less expensive than the intravenous route. This study was designed as a clinical trial to evaluate the early and late outcome of the treatment with oral ibuprofen to determine its efficacy and safety in closure of PDA in premature infants.

Methods

Thirty eight premature neonates with gestational age below 37 weeks born at Amir Hospital, Semnan, Iran were recruited prospectively. The study was approved by the Ethics Committee of the Semnan University of Medical Sciences and has the Iranian Registry of Clinical Trial code of: IRCT 2013071113022N2.

The infants were enrolled in the study only after written parental consent had been obtained.

Neonates who were admitted to the study were enrolled when the following criteria were met:

1) Gestational age <37 weeks, 2) postnatal age between 24 and 96 hours, 3) echocardiographic evidence of hemodynamically significant PDA (left atrium/aortic root diameter ratio >1.4/1 or ductal size >1.5 mm) (9).

Exclusion criteria included echocardiographic evidence of congestive heart failure with left ventricular shortening fraction below 28%, evidence of congenital heart disease, existence of congenital anomalies, intraventricular hemorrhage of grade 3 according to the classification by Papile et al (10) within previous 24 hours, serum urea nitrogen concentration >50 mg/L, platelet count < 60000/ml, a tendency to bleed (defined as presence of hematuria, blood in the endotracheal aspirate, gastric aspirate, or stools and/or oozing from puncture sites), or hyperbilirubinemia necessitating exchange transfusion and neonates whose mothers had taken anti-inflammatory agents during the last days of pregnancy.

Study Design

All premature infants who were born between October 2012 and March 2013 and met the entry criteria, first underwent echocardiography and cranial ultrasonography, after which they were divided randomly into two groups: Nineteen were treated with oral ibuprofen (Saha Drug Factory, Iran) 10mg/kg administered through a feeding tube, a second and a third dose of oral ibuprofen 5mg/kg were administered 24 and 48 hours after

the first dose.

Nineteen neonates were treated with fluid restriction by limiting the calculated daily serum to two third of the required maintenance dose.

Respiratory support was given by simultaneous intermittent mechanical ventilation (SIMV) or oxygen supplements by nasal continuous pulmonary airway pressure (CPAP). Prophylactic antibiotics were started on admission and stopped after 5 days if blood cultures were negative.

Echocardiography

Color Doppler echocardiography (Agilent Image Point HX, Transducer P7510, Massachusetts, USA) was performed on all infants who were clinically suspected of having PDA. This was conducted by a pediatric cardiologist who was blind to the child's name and 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 more than 1.5 mm or the left atrium to aortic root ratio was >1.4/1.

Echocardiography was repeated on 3rd and 7th day, 3rd month and 6 month after birth for all the 38 infants and PDA closure and pulmonary artery pressure were measured.

Mean pulmonary arterial pressure was measured by echocardiography according to guidelines of American Society of Echocardiography applying following formula:

$MPAP = 4 \times PRV^2 + RAP$ (≥ 25 mmHg) (MPAP: Mean Pulmonary Arterial Pressure) (PRV=Peak Pulmonary Regurgitation Velocity), (RAP: Right Atrial Pressure) (11).

Cranial Ultrasonography

Cranial ultrasonography was performed at the age of one week and one month after birth for detection of intraventricular hemorrhage and periventricular leukomalacia.

Ophthalmologic Examination

All the neonates were examined by an ophthalmologist who was blind of the infants' name and study group for retinopathy of prematurity at the discharge time and the age of one month.

Data including the duration of hospital stay, intrapulmonary hemorrhage, and duration of respiratory care with SIMV, duration of oxygen dependency under CPAP, neonatal sepsis and age of the infant at discharge were recorded prospectively

Table 1. Baseline characteristics and outcome of the study infants

Characteristic	Study Group		P value
	Ibuprofen n(%)	Fluid restriction n(%)	
<i>Gestational Age(Week)</i>			
28-30	2(10.5)	2(10.5)	0.817
31-33	1(5.3)	1(5.3)	
34-36	9(74.4)	10(52.6)	
37-38	7(36.8)	6(31.6)	
Birth Body Wight(gr)			
<1000	1(5.3)	1(5.3)	0.583
1001-1500	1(5.3)	3(15.8)	
1501-2000	4(21.1)	4(21.1)	
2001-3000	10(52.6)	8(42.1)	
>3000	3(15.8)	3(15.8)	
Hours under Nasal CPAP			
No need	17(89.5)	9(47.3)	0.005
<24	-	7(36.8)	
24-48	-	1(5.3)	
48-72	-	2(10.5)	
>72	2(10.5)	-	
Hours under Ventilator(SIMV)			
No need	17(89.5)	17(89.5)	1.000
<24	-	-	
24-48	-	1(5.3)	
48-72	-	1(5.3)	
>72	2 (10.5)	-	

and compared between the study groups.

Statistical Analysis

Continuous data such as weight, gestational age, various treatment modalities, IVH, ROP, pulmonary hemorrhage, pulmonary artery pressure, duration of respiratory care, duration of oxygen requirement and neonatal sepsis are presented as mean± standard deviation.

Results

The baseline characteristics of the 38 studied infants are presented in Table 1. The rate of PDA closure was 100% in the ibuprofen group, whereas 84.1% in the group with fluid restriction ($p=0.23$).

There was no reopening of the ductus after closure was achieved. No infant required surgical ligation of the ductus. No retinopathy of prematurity was detected in the infants and no periventricular leukomalacia was detected by cranial ultrasonography.

One of the infants in each group developed intraventricular hemorrhage of grade one that was relieved at the age of one month ultrasonography.

At the echocardiography before treatment no increase in pulmonary artery pressure was detected and in further echocardiography at one week, three months and six months no increase of pulmonary artery pressure was observed. Early outcome results are presented in Table 2.

Outcome and side effects

Two infants in the ibuprofen group and one in the fluid restriction group developed pulmonary hemorrhage ($p=1.00$). One of them had birth body weight of 1000 gram and gestational age of 27 weeks and developed bleeding from the intratracheal tube after the second dose of ibuprofen and was treated with intratracheal epinephrine, and intravenous vitamin K and fresh frozen plasma and the bleeding was relieved ultimately. The other infant was 1500 gram with gestational age of 30 weeks and developed pulmonary and gastric bleeding after first ibuprofen dose and received the same treatment modality. After bleeding was stopped successfully the next doses of ibuprofen were given to the infant.

The infant in the fluid restriction group was 30 weeks and weighed 1100 gram and developed pulmonary hemorrhage 4 days after admission and was treated successfully with the same modality. None of the infants developed sepsis or nosocomial infection during hospital stay.

Discussion

There have been concerns about side effects and complications occurring during and after treatment of PDA with oral ibuprofen. The study was performed to determine the efficacy and early and

Table 2. Early outcome at hospital

Outcome	Study Group		P value
	Ibuprofen Mean±SD	Fluid restriction Mean± SD	
Days at hospital	5.2±2.1	5.2±3.9	1.000
Days at NICU	4.3±7.2	6.9±7.7	0.053
Days needed to arrive at Birth weight	11.2±3.5	11.2±3.4	0.931

SD: Standard Deviation

outcome of this treatment modality.

As PDA closure was achieved in all of the infants in the ibuprofen group in comparison to the efficacy of 84.2% ($p=0.23$) in the control group, we consider this treatment as efficient. Other studies also show similar results: 95% closure rate in the study of Heyman (2003) (12) and in a large study conducted by Ohlsson (2013) reviewing twenty seven studies, there was a decreased risk of failure to close a PDA with oral ibuprofen compared with intravenous ibuprofen, three studies ($n=236$) typical RR 0.37(95% CI 0.23 to 0.61); typical risk difference RD -0.24(95%CI -0.35 to -0.13); number needed to benefit 4(95% CI 3 to 8) (13).

In our study IVH grade I was observed in one infant of each group before study and no further hemorrhage occurred during the study. No case of gastrointestinal bleeding, necrotizing enterocolitis or renal dysfunction was observed in the study group.

Guzoglu N et al (2014) observed no significant differences in regional oxygen saturation and fractional oxygen extraction of renal and mesenteric tissues in PDA and control infants ($p>0.05$). Ibuprofen treatment did not negatively influence renal and mesenteric oxygenation and extraction in infants with PDA ($p>0.05$) (14).

In the study of Lee et al (2012) the incidence rates of oliguria and elevated serum creatinine were significantly lower in the ibuprofen group ($p=0.002$ and $p=0.022$, respectively). There was no significant difference in incidence of upper gastrointestinal hemorrhage or necrotizing enterocolitis between the ibuprofen and indomethacin groups (17.3% versus 23.9%; 3.8% versus 11.3%) (15).

Ohlsson reported that the risk of necrotizing enterocolitis was reduced for ibuprofen (15 studies ($n=865$); typical RR 0.68 CI 0.47 to 0.99); typical RD -0.04 (95%CI -0.08 to -0.00; $p=0.004$) (13).

Therefore authors conclude that ibuprofen is as effective as indomethacin in closing PDA and reduces the risk of NEC and transient renal insufficiency. Given the reduction in NEC ibuprofen currently appears to be the drug of choice.

Regarding Oxygen therapy, in case group 13 patients (68.4%) and in control group 7 patients (36.8%) required oxygen therapy in incubator ($p=0.163$). Ohlsson reported that the duration of ventilator support was reduced with ibuprofen (oral or intravenous) compared to oral or intravenous indomethacin. (Six studies, $n=471$) mean difference (MD) -2.35 days (95%CI -3.71 to -0.99); $I^2=19\%$ (13).

Regarding late outcome we observed no case of pulmonary hypertension at hospital stay and none after longer follow up after three and six months echocardiography. Furthermore, no case of ROP was observed at one month follow up examination and no case of PVL was detected at one month ultrasonography.

In a study performed by Bellini et al (16) (2006) one case of pulmonary hypertension was observed in a 32 weeks premature neonate after ibuprofen therapy for PDA closure. The PAP was increased to about 50mmHg but was relieved with inhaled nitric oxide therapy and on day 5 their case died because of generalized sepsis. The postmortem autopsy showed no thickening of arterial vessels or intimal-medial alterations. This severe side effect has never been observed in multicenter, randomized, double blind controlled trials, or in recent reviews or Meta-analysis of L-lysine ibuprofen use (16).

Sangtawesin et al (2006) reported no case of PVL, bronchopulmonary dysplasia and pulmonary hypertension in their study (8).

There was no statically significant differences in mortality, reopening of the ductus, need for surgical duct ligation, duration of ventilator support, duration of supplementary oxygen, pulmonary hemorrhage, pulmonary hypertension, chronic lung disease (CLD), IVH, PVL, NEC, intestinal perforation, gastrointestinal bleed, time to full enteral feeds, time to regain birth weight, ROP, sepsis and duration of hospitalization in a large systematic review conducted by Ohlsson (17).

The available data support the use of oral ibuprofen for the treatment of a PDA and this drug reduces the risk of NEC and transient renal insufficiency.

iciency. Given the reduction in NEC, ibuprofen currently appears to be the drug of choice (13).

The results of late outcome also supports the use of this drug, however longer survival rates without impairment at 18 months and at the age of school entry are also recommended.

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Conflicts of interest: We attest that we have herein disclosed any and all financial or other relationships that could be construed as a conflict of interest.

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