Patent Ductus Arteriosus at low birth weight preterm infants and perinatal infection

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Abstract

Aims: The aim of this study was to compare the efficacy and safety of oral versus intravenous ibuprofen for the pharmacological closure of patent ductus arteriosus (PDA) in low birth weight (LBW) preterm infants and assess the impact of perinatal infection to pharmacological closure of PDA in LBW preterm infants.
Methods: A randomized, single-blinded, clinical trial included 68 premature infants with significant PDA confirmed through cardiac ultrasound at the "Koço Gliozheni" maternity hospital in Tirana, Albania, during January 2010-December 2012. Infants were randomly assigned to receive either intravenous (n=32) or oral ibuprofen (n=36) at an initial dose of 10 mg/kg, followed by 5 mg/kg after 24 hours and after 48 hours. The rate of ductal closure, reopening, the need for surgical ligation, and the patients' clinical course were recorded.
Results: After the first treatment cycle, the PDA closed in 83.3% of the patients receiving oral vs. 71.8% of those receiving intravenous ibuprofen. 16.6% of the patients in the oral group required a second cycle of treatment, compared with 28.1% in the intravenous group; all these cases had clinical signs of infection and positive bloodculture. No reopening of the ductus after its closure was noticed. Furthermore, there were no patients with oliguria.
Conclusions: Oral ibruprofen showed a similar rate of ductal closure and renal tolerance, but fewer adverse effects compared to intravenous ibuprofen. Association of PDA with perinatal infection has a negative impact in pharmacological closure of the ductus, increasing the need for a second treatment cycle and surgical ligation. Larger comparative studies are needed to replicate these findings.

Keywords: *intravenous ibuprofen, oral ibuprofen, patent ductus arteriosus, perinatal infection, prematurity.*

Introduction

Patent ductus arteriosus (PDA) is extremely common in very premature infants and untreated symptomatic PDA may be associated with chronic lung disease (1). Clinical and epidemiological data strongly suggest that infections, either prenatal or nosocomial, and the presence of a patent ductus arteriosus (PDA) play a major role in the neonatal mortality and morbidity (2-4). For this reason, efforts to prevent this complication in low birth weight infants should include an aggressive approach to the prevention and treatment of prenatal and neonatal infections and an early closure of the PDA. Pharmacological closure of PDA with indomethacin or ibuprofen, which are both prostaglandin inhibitors, has remained the mainstay of treatment in premature infants over the last three decades (5,6). In search of an explanation for the interaction between neonatal infection and PDA, it was observed that the presence of a systemic infection in the premature infant adversely affects permanent closure of the ductus, often inducing ductal opening after the first week of life and failure to respond to medical treatment with indomethacin (7). A likely explanation for this interaction is the elevated serum levels of prostaglandins and tumor necrosis factor (TNF) observed in infants with infections. In addition, infants with serious infections frequently have complications that prevent or delay the medical or surgical treatment of the PDA. As a result, the ductus remains open for prolonged periods of time, maintaining an increased pulmonary blood flow, high capillary pressure, and increased lung fluid. Furthermore, when both complications (infection and PDA) occurred at the same time, they produced a synergistic interaction, further increasing the risk for developing chronic lung disease (CLD). As a consequence of the left-to-right shunting through the PDA, pulmonary blood flow and lung fluid increases, negatively affecting lung function and gas exchange, and thereby increasing the risk for CLD. The presence of a PDA has also been associated with elevated concentrations of myeloperoidase in the tracheobronchial fluid, suggesting that the increased pulmonary blood flow may result in damage of the pulmonary endothelium and adhesion and migration of polymorphonuclear cells (PMNs) into the lung tissue (7,8). Sepsis is reported to increase the risk of late ductal reopening, and failure of PDA closure probably relates to the associated increased levels of prostaglandin and tumour necrosis factor á (9). Concerns have been raised that indometacin may predispose very low birth weight neonates to sepsis (10). Considerable biological plausibility thus exists to explain the influence of significant PDA and sepsis on feed tolerance in preterm neonates. PDA and sepsis are possibly markers of prematurity, and a prolonged interval between starting feed and full enteral feed simply reflects the reluctance to start or continue feeds in the presence of such perceived risk factors for feed intolerance and necrotising enterocolitis (NEC) (11,12). A temporary closure and reopening of the duct has been reported as being associated with severe infection and sepsis (5).

Methods

The study was designed as a prospective, randomized, single blinded, study. The study was conducted in the neonatal intensive care unit (NICU) of the University Hospital for Obstetrics and Gynecology "Koço Gliozheni" in Tirana, Albania, from January 2010 to December 2012. This study was approved by the Faculty of Medicine and the Neonatology Department.

The study enrolled preterm infants with a gestational age 28-32 weeks, birth-weight d"2000g, postnatal age 48-96 hours, RDS treated with mechanical ventilation [CPAP or intermittent positive pressure ventilation (IPPV)] with additional oxygen requirements above 30% and one of the following echocardiographic criteria of a duct size >1.5 mm: a left atrium-to-aorta ratio >1.5, left-to-right shunting of blood in addition to signs of PDA.

GA was assessed by obstetrical dating criteria or, when obstetrical data was inadequate, by Ballard examination.

Exclusion criteria were major congenital abnormalities, right-to-left ductal shunting, life-threatening infection, grade 3 or 4 intraventricular hemorrhage, oliguria of less than 1 ml /kg /h during the preceding eight hours, serum creatinine concentration in excess of 1.6 mg/ dl, blood urea nitrogen in excess of 60 mg/ dl, thrombocyte count of less than 60 000/mm^3, clinical bleeding tendency as revealed by haematuria, blood in the gastric aspirate or in the stools, blood in the endotracheal tube aspirate, oozing from venous or capillary

puncture sites, hyperbilirubinemia for which exchange transfusion was required and pulmonary hypertension.

All infants who met the entry criteria first underwent echocardiography and cranial ultrasonography, after which they were treated with oral ibuprofen (Brufen, Abbot S.r.l, Italy Algofren) at 10 mg/ kg dose via an orogastric tube, which was flushed with 1 mL of sterile water to ensure delivery of the drug, or intravenous ibuprofen (Pedea, Orphan Europe; a vial of 2 mL containing 10 mg of ibuprofen) which was infused over a 15-minute period with a syringe pump, the line was subsequently being flushed with saline.

The two imaging procedures were again performed 24 hours after each ibuprofen dose. When the PDA was still hemodynamically significant, as demonstrated by echocardiography, and there was no evidence of deterioration in brain ultrasonography, a second dose of ibuprofen 5 mg/ kg was administered. A third equivalent dose was given after another 24 hours if deemed necessary. Cranial ultrasound was repeated 1 week after the last ibuprofen dose and again before discharge from the ward. Hematochemical analyses were preformed daily in the unit during the first days of life.

RDS was treated with respiratory support (CPAP,intermittent mechanical ventilation or high-frequency ventilation), oxygen supplements, and surfactant (Curosurf, Chiesi, Italy; a vial of 1.5 mL containing 120 mg) was administered intratracheally at the dosage of 100 to 200 mg/ kg. Prophylactic antibiotics were started on admission and stopped after 5 days if blood cultures were negative. Birth weight, gestational age, and clinical outcomes were recorded prospectively.

Occurrence of any of the following conditions was enough to discontinue treatment: IVH grade 3–4, renal failure, NEC, and gastrointestinal bleeding (GEB).

The color Doppler echocardiografi was conducted by a pediatric-cardiologist who was not awere to the child's name and the treatment being given. PDA was considered echocardiographically significant when the ductal size was >1.5 mm or the left atrial-to-aortic root ratio was >1.4. We evaluated these parameters before the first dose and 24 hours after each dose of ibuprofen, never exceeding 3 doses in total. One day after the third treatment, an echocardiographic evaluation was performed by the same pediatric- cardiologist to determine the success of the treatment and the need for a second course via the same route.

Before and 24 hours after treatment, all patients were evaluated with a complete blood count, renal function tests (serum creatinine level, blood urea nitrogen and urine output), cranial ultrasonography, and echocardiography. All infants continued their current enteral feeding during the treatment.

Sample size and statistical analysis

We calculated that a study group of 68 patients would be necessary for detection of a difference of at least 25 percentage points in the closure rate between the oral ibuprofen and intravenous ibuprofen groups, assuming a closure rate of 70% with intravenous ibuprofen, with a P value of 0.05 and a study power of 85%.

SPSS for Windows (SPSS version 19.0, Chicago, IL), and Minitab (Minitab version 15.0, State College, PA) were used to conduct the statistical analyses.

The data are presented as means ± standard deviations (numerical variables), or frequencies (absolute number and their respective percentages – categorical variables).

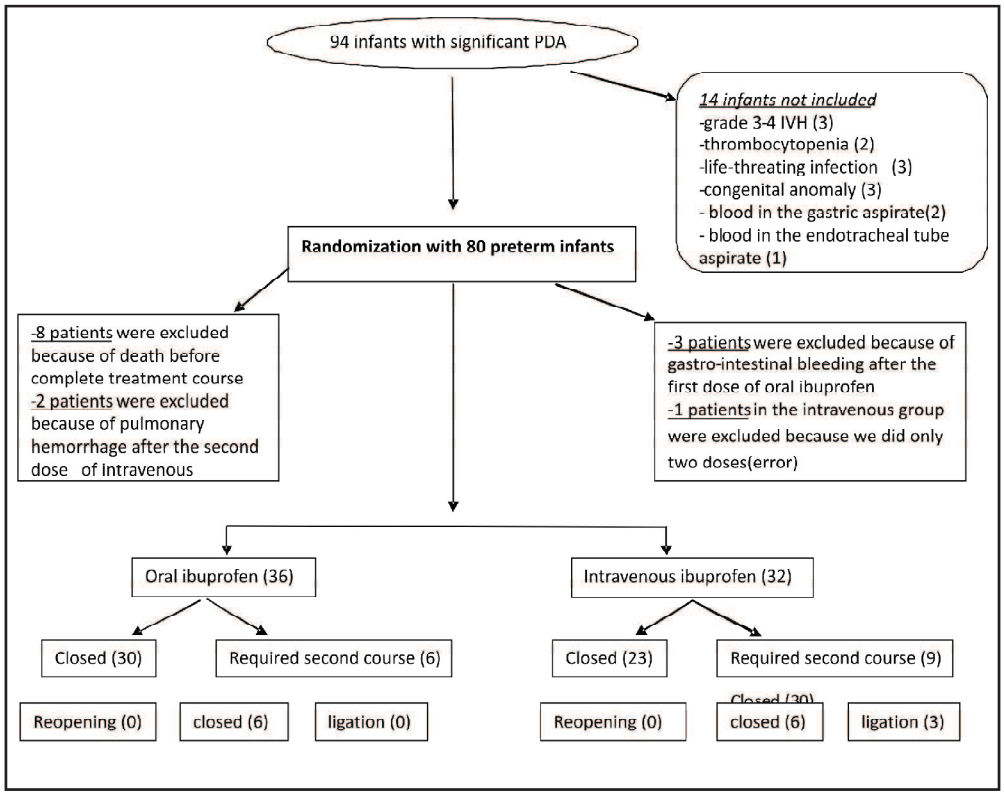
Paired-samples *t*-test and independent-samples *t*-test were used for continuous variables. Conversely, chi-square test was used to compare the proportion of patients experiencing the secondary outcomes of PDA closure. In all cases, a p-value of d"0.05 was considered statistically significant.

Results

A total of 168 premature infants at gestational age <32 weeks and birth weight d"2000 g and SDR were admitted to our NICU, from January 2010 to December 2012 and underwent an echo-cardiografic Doppler ultrasound evaluation at the age of 48-96 hours. The entire study protocol was completed for 80 patients because of exclusion for various reasons (Figure 1).

Baseline characteristics were similar between the two groups in the first 96 hours (Table 1).

Figure 1. Study design



After the first course of the treatment, the PDA closed in 30 (83.3%) of the patients assigned to the oral
ibuprofen group versus 23 (71.8%) of those enrolled in the intravenous ibuprofen group. Six patients (16.6%) in the oral ibuprofen group required a second course of drug therapy, compared with 9 (28.1%) in the intravenous ibuprofen group. There was no reopening of the ductus after closure was achieved. The cumulative closure rates were higher in both groups, and only three patients (9.3%) in the intravenous ibuprofen group had surgical ligation.

Table 1. Baseline characteristics of study participants

Variable	Oral group (n=36)	Intravenous group (n=32)
Gestational age, weeks		
28.1-30.0 weeks	19 (52.7%) *	18 (56.2%)
30.1-32.0 weeks	17 (47.2%)	14 (43.7%)
Birth weight (in grams)		
<750g	2 (5.5%)	0 (0%)
751 -1000g	7 (19.4%)	6 (18.7%)
1001 -1500g	15 (41.6%)	19 (59.3%)
1501-2000g	12 (33.3%)	7 (21.8%)
Gender		
Male	22 (61.1%)	15 (46.8%)
Female	14 (38.8%)	17 (53.1%)
Delivery by cesarean section	20 (55.5%)	14 (43.7%)
Antenatal indomethacin	0 (0%)	0 (0%)
Antenatal glucocorticoid	28 (77.7%)	18 (56.2%)
Mean ductal diameter (mm)	2.1	1.9

* *Absolute numbers and percentages (in parenthesis) within the respective groups.*

In the evaluation of renal tolerance, none of the patients had oliguria. The serum creatinine levels and plasma blood urea nitrogen after the treatment did not differ significantly between the groups. Renal function test results before and after the second course of each drug did not differ significantly within or between the groups (Table 2).

Table 2. Renal function results among the study participants

Parameter	Oral group (n=36)	Intravenous group (n=32)	P
Plasma blood urea nitrogen(mg/dl)			
Day 1	30.7 ± 14.8 *	30.4 ± 13.7	0.900
Day 2	30.3± 14.2	30.6 ± 14.0	0.890
Mean plasma creatinine (mg/dL)			
Day 1	1.07 ± 0.24 *	1.09 ± 0.24	0.060
Day2	1.20 ± 0.95	0.97±0.45	0.070
Oligoanuria (ml/kg/h)			
Day1	0 (0%) †	0 (0%)	
Day2	0 (0%)	0 (0%)	
Infection			
Need for a second treatment course	6 (16.6%) †	9 (28.1%)	
Need for surgical ligation	0 (0%)	3 (9.3%)	

* *Mean value ± standard deviation.*

† *A bsolute number and percentage within the respective group (in parenthesis)*

15 patiens needed a second treatment course and they were all(100%) with clinical signs of infection and positive bloodculture and the same result was for the 3 (9%) patients who needed surgical ligation.

Discussion

Intravenous ibuprofen is not available in most countries (and in our country to), and is more expensive than the oral form. If oral ibuprofen were as efficient as intravenous ibuprofen with no greater adverse effects, its simple administration and lower cost would be important advantages. Our study was designed with sufficient power for determining whether oral and intravenous ibuprofen treatments are equally efficacious and safe in PDA closure in premature infants with respiratory distress syndrome (RDS). Our results showed oral ibuprofen to be effective and safe in PDA closure, with 30 of our 36 (83.3%) study infants achieving a successful outcome. The rate of closure in the group assigned to intravenous ibuprofen was similar to rates previously reported (4,11). Some trials on the use of oral ibuprofen for closure of PDA have been recently published (13-15). All studies had small sample sizes. Aly (16) in a randomized pilot study, reported that PDA was closed in 7 of 9 premature infants (d”35 weeks) given oral ibuprofen and in 10 of 12 premature infants given intravenous indomethacin ($P = 0.75$). Fakhraee, (17) in a randomized study, reported that PDA was closed in all of 18 premature infants (d”34 weeks) given oral ibuprofen and in 15 of 18 premature infants given oral indomethacin ($P > .05$). Efficacy of oral ibuprofen compared with intravenous indomethacin, was reported by Supapannachart et al. (18) and Chotigeat et al. (19) as well. In nonrandomized open trials, Heyman et al. (20) and Cherif et al. (21) reported a ductal closure with oral ibuprofen respectively in 21 (95.4%) of 22 patients, 38 (95%) of 40 patients, and in 11 (84.6%) of 13 patients. The authors concluded that oral ibuprofen might constitute a feasible alternative in the treatment of PDA. Another study investigated the efficacy of indomethacin and ibuprofen given to larger premature infants (d”32 weeks) at the age of 2-4 days. They reported that the closure rate was similar (66% and 70%, respectively) after the first course and that there was no significant difference in side effects, although ibuprofen was associated with significantly less impairment of renal function (11). The previous study comparing oral and intravenous ibuprofen enrolled 64 preterm infants. That trial

demonstrated that the rate of ductal closure tended to be higher in the oral group (84% versus 62%). This study was not powered to detect differences in complications (20). Two studies increase the number of infants randomized and expand the information about the safety and efficacy of oral ibuprofen in more mature very LBW infants (22,23). We hope that our study will give its contribution in this regard too.

Since renal tolerability of ibuprofen on renal function in the neonate is a major argument in favour of its use in the treatment of PDA (22,23), our study expands our information about the safety and efficacy of oral ibuprofen in more mature VLBW infants.

Serum creatinine levels and uremia in our patients were within normal range at all times, so there was no contraindication for a second 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 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 they were treated with oral ibuprofen or intravenous ibuprofen. This is the first experience that we have with ibuprofen (oral or intravenous) for treatment of PDA in preterm infants.

Conclusion

Our data indicate that, for preterm infants especially for LBW infants, the rate of early ductal closure was comparable and the adverse effects were fewer with oral ibuprofen in comparison to the intravenous route. Association of PDA with perinatal infection has a negative impact in pharmacological closure of the ductus, increasing need for a second course and for surgical ligation. The oral form was as safe as the intravenous form in terms of renal tolerance. Larger comparative studies are needed to replicate these findings.

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