ORAL VERSUS INTRAVENOUS IBUPROFEN FOR THE EARLY CLOSURE OF PATENT DUCTUS ARTERIOSUS IN LOW BIRTH WEIGHT PRETERM INFANTS

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ABSTRACT

Background

Patent ductus arteriosus (PDA) is common in very premature infants. Pharmacological closure of PDA with indomethacin, a prostaglandin inhibitor, has remained the mainstay of treatment in premature infants over the last three decades. Intravenous ibuprofen was recently shown to be as effective and to have fewer adverse reaction in preterm infants. If equally effective, then oral ibuprofen for PDA closure would have several important advantages over the intravenous route.

This study was designed to assess the efficacy and safety of oral ibuprofen and intravenous ibuprofen for the early pharmacological treatment of PDA in LBW preterm infants with respiratory distress syndrome.

Methods

A randomized, single-blinded, controlled study was performed on premature neonates at the neonatal care unit of the University Hospital for Obstetrics and Gynecology"Koco Gliozheni", Tirana, Albania, from January 2010 to December 2012. The study enrolled 68 preterm infants with gestational age between 28-32 weeks, birth weight ≤ 2000 g, postnatal age 48-96 h, and had echocardiographically confirmed significant PDA. The preterm infants received either intravenous or oral ibuprofen randomly as an initial dose of 10 mg/kg, followed by 5 mg/kg at 24 and 48 h. After the first dose of treatment in both groups, echocardiographic evaluation was performed, to determine the need for a second or third dose. The rate of ductal closure, adverse effects, complications, and the patient's clinical course were recorded.

Results

All patients were born after 28 until 32 weeks' gestation. 36 patients were treated with oral ibuprofen and 32 with intravenous ibuprofen in this period. 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 (p = 0.355). There was no difference between treatment groups in demographics or baseline renal function. In the evaluation of renal tolerance, none of the patients had oliguria. There were no significant differences with respect to complications during the stay.

Conclusions

In low birth weight infants, the rate of early ductal closure with oral ibuprofen is at least as good as with the intravenous route. Oral ibuprofen is associated with fewer adverse effects.

UDC CODE & KEYWORDS

■ UDC: 100 – 110 ■ Patent ductus arteriosus ■ Ibuprofen ■ LBW infants ■ Adverse effects ■ Renal function

INTRODUCTION

Patent ductus arteriosus (PDA) is a common occurrence in very low birth weight (VLBW, ≤1500 g) infants, which often causes significant morbidities. Left-to-right shunting through the ductus may increase the risk of intraventricular hemorrhage [1,2], necrotizing enterocolitis [3], bronchopulmonary dysplasia, and death [4,5]. Pharmacological closure of PDA with indomethacin, a prostaglandin inhibitor, has remained the mainstay of treatment in premature infants over the last three decades. Successful pharmacological closure of PDA with indomethacin was first reported in 1976, with subsequent reports that indomethacin reduced neonatal morbidity [6,7]. However, indomethacin may lead to complications such as transient or permanent renal dysfunction [8,9], necrotizing enterocolitis, and reduced cerebral oxygenation [10]. These indomethacin-related complications have prompted researchers to seek safer pharmacological treatment for closure of PDA. In recent years another cyclooxygenase inhibitor, ibuprofen, has been proposed for the treatment of PDA, and several randomized controlled trials have shown it to be as efficacious as indomethacin, with possibly fewer adverse effects [11]. Recently, ibuprofen lysine was approved by the US Food and Drug Administration (FDA) for use in treatment of PDA for premature infants. However, since renal perfusion, glomerular filtration rate (GFR) and diuresis in early neonatal life strongly depend on the vasodilator effects of prostaglandins (PGs) on the afferent glomerular arterioles [5,12,13], ibuprofen, as is the case with other COX inhibitors, may not be exempt from causing some renal undesirable effects [14]. Renal dysfunction in the preterm newborn often results from the combined effect of prerenal factors that may reduce renal perfusion and/or oxygenation, and prematurity, increasing the risk of an acute renal failure during the first weeks. Moreover, respiratory distress syndrome (RDS) that needs mechanical ventilation with a high mean airway pressure and/or continuous positive airway pressure may exert a deleterious effect on renal hemodynamics [15]. The intravenous preparations of indomethacin and ibuprofen are available only in some medically resource-rich countries and at exorbitant prices, but this is impossible for my country with low budget. We don't offer surgical ligation in neonatal period and so we are interested for the pharmacological closure of PDA in preterm infants, especially for oral ibuprofen because is not expensive.

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Materials and methods

The study was designed as a prospective, randomized, one blind, study. The study was conducted in the neonatal intensive care unit of the University Hospital for Obstetrics and Gynecology"Koco Gliozheni", Tirana, Albania, between January 2010 to December 2012. This study was approved by the local ethics committee, and infants were enrolled in the study after written parental consent.

Inclusion criteria

All premature newborns, born between 28 weeks to ≤ 32 weeks' gestation, admitted to the neonatal intensive care unit, were eligible for this study, if they met the inclusion criteria:

- birth weight ≤ 2000g,
- postnatal age between 48 and 96 hours,
- PDA with evidence of ductal shunting documented by echocardiogram,
- RDS requiring > 25 % oxygen supplementation.

Exclusion criteria:

- major congenital malformations and/or chromosomal anomalies,
- right-to-left shunting,
- HIV grade 3-4,
- proven congenital bacterial infection,
- renal failure or oliguria defined as urine flow rate < 1 mL/kg/h in the 8 hours prior to randomization (anuria was acceptable if infant was within first 24 hours of life),
- platelet count < 60,000/mL,
- clinical bleeding tendency (i.e., oozing from puncture sites),
- the serum creatinine levels <1.6 mg/ %,
- blood urea nitrogen <60 mg/%,
- hiperbilirubinemia necessitating exchange transfusion,
- expected survival > 48 hours in the opinion of the attending neonatologist,
- approved by the medical director or study coordinator.

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

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) 10 mg/kg was given 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) was infused over a 15 minute period with a syringe pump, and the line was subsequently flushed with saline. 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.

Tolerance was assessed daily during the week after the beginning of treatment by clinical examination (tendency to bleed, abdominal bloating, urine output), cranial ultrasound examination (IVH, change in grade), and laboratory tests (serum creatinine and serum urea nitrogen levels). Oliguria was defined as a urine output of 1 mL/kg per hour or less during a 24-hour collection period. Occurrence of any of the following conditions was enough to discontinue treatment: IVH grade 3 – 4, renal failure, NEC, and gastrointestinal bleeding (GEB). The 2 imaging procedures were again performed 24 hours after each ibuprofen dose. 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.

For all patients enrolled in the study, fluid intake was begun at 70 mL/kg per day with increases by increments of 10 mL/kg each day to a maximum of 120 mL/kg per day by the end of the study. RDS was treated with respiratory support (ventilatory support was imposed by the severity of the respiratory distress and included nasal continuous positive airway pressure, intermittent positive pressure ventilation, and high-frequency oscillatory 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 2 days if blood cultures were negative.

Echocardiography

Color Doppler echocardiography (Vivid 3 sonde 7.5Mhz) was performed on all infants who were clinically suspected of having PDA. This was conducted by a technician under the supervision of a cardiologist who was blind to the child's name and the treatment being given. PDA was considered echocardiographically significant when the ductal size was > 1.5 mm, the left atrial-to-aortic root ratio was > 1.4 and left-to-right shunting. 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 to determine the success of the treatment and the need for a second course via the same route.

During the first week, all patients enrolled in the study were prospectively assessed for ductal closure, number of doses required, mode and duration of ventilation, surfactant treatment, renal failure, IVH [16], NEC [17], and GEB.

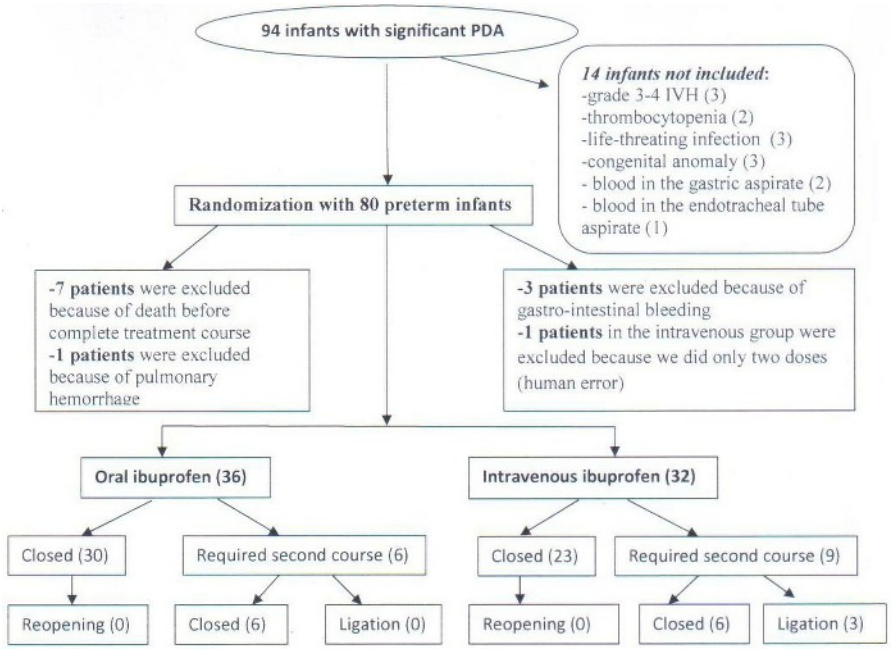
Statistical analysis

We calculated that a study group of 68 patients would be necessary for the study to be able to detect 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 power of 85%. Continuous data are presented as mean ± SD. Comparisons between groups were performed by using independent - samples t test for parametric continuous variables; the χ^2 was used for categorical variables. A p value of < 0.05 was considered significant.

Results

The number of patients who were eligible for the study, who were excluded and who were randomly assigned to receive oral ibuprofen or intravenous ibuprofen, are shown in Fig.1.

Figure 1: Flow chart of the study



Source: Authors

There were no significant differences between the 2 groups in baseline clinical characteristics (Table 1).

Table 1: Baseline Characteristics of the Study Patients

Baseline characteristics	Oral (36)	Venous (32)
Gestational age, wk, n (%)		
28.1- 30 week	19 (52.7%)	18 (56.2%)
30.1- 32 week	17 (47.2%)	14 (43.7%)
Birth weight, g, n (%)		
<750g, n	2 (5.5%)	0 (0%)
751-1000g, n	7 (19.4%)	6 (18.7%)
1001- 1500g, n	15 (41.6%)	19 (59.3)
1501- 2000g, n	12 (33.3%)	7 (21.8%)
Gender		
male, n	22 (61.1%)	17 (53.1%)
female, n	14 (38.8%)	14 (43.7%)
Delivery by caesarian section, n (%)	20 (55.5%)	14 (43.7%)
Antenatal indometacine, n (%)	0 (0%)	0 (0%)
Antenatal glucocorticoids, n (%)	26 (72.2%)	18 (56.2%)
Perinatal asphyxia, n (%)	11 (30.5%)	9 (28.1%)
Mean ductual diameter, mm	1.9	2.1

Source: Authors

Efficacy of treatment

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 (p = 0.355). 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.

Early outcome

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 after the first treatment course (Table 2). Furosemide was not used during the first week of life.

Table 2: Evaluation of renal function tests after first course of treatment

	Oral ibuprofen			Intravenous ibuprofen		
Measurement	Before	After	P value	Before	After	P value
Mean plasma creatinine (mg/%)	1.10 ± 0.25	1.07± 0.23	.06	1.08 ± 0.22	1.85±0.24	.92
Plasma blood urea nitrogen (mg/%)	31.6 ± 10.5	31.3 ± 8.7	.91	30.8 ± 7.7	31.6 ± 9.9	.68
Urine output (mL/kg/h)	3.2± 1	2.8 ± 0.8	.06	3.08 ± 0.85	3.3± 0.5	.08

Source: Authors

Outcome of the study infants are presented in Table 3.

Table 3: Outcome of the study infants

Outcome variables	Oral (n=36)	Intravenous(n=32)
Death, n (%)	4 (11.1%)	6 (18.7%)
NEC, n (%)	0 (0%)	0 (0%)
GEB, n (%)	3 (8.3%)	0 (0%)
IVH, grade 1-2	4 (11.1%)	5 (15.6%)
IVH, grade 3-4	1 (2.7%)	1 (3.1%)
Surfactant treatment	24 (66.6%)	20 (62.5%)
Pulmonary hemorrhage	0 (0%)	2 (6.2%)

Source: Authors

There were no differences between groups in the incidence of IVH 1–2 [oral (n = 4) versus intravenous (n = 5)], IVH 3–4 [oral (n = 1) versus intravenous (n = 1)], NEC [oral (n = 0) versus intravenous (n = 0)], GEB [oral (n = 3) versus intravenous (n = 0)] and pulmonary hemorrhage [oral (n = 0) versus intravenous (n = 2)].

After the second treatment course the closure rate was 100% in oral group and only three patients in the intravenous group needed surgical ligation.

Survival at 1 month tended to be similar in the two groups (88.9% versus 81.3 %). Surfactant treatment was similar in the two groups [24 (66.6%) versus 20 (62.5%)].

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 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. There are two or three randomized study, to our knowledge, comparing oral ibuprofen and intravenous ibuprofen in closure of PDA. The rate of closure in the group assigned to intravenous ibuprofen was similar to rates previously reported [5,12]. Some trials on the use of oral ibuprofen for closure of PDA have been recently published [17,18,29]. All studies had small sample sizes. Aly [20] in a randomized pilot study, reported that PDA was closed in 7 of 9 premature infants (≤35 weeks) given oral ibuprofen and in 10 of 12 premature infants given intravenous indomethacin (P = .75). Fakhraee, [21] in a randomized study, reported that PDA was closed in all of 18 premature infants (≤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 [22] and Chotigeat et al, [23] as well. In nonrandomized open trials, Heyman et al, [24] and Cherif et al, [17] 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. Van Overmeire et al. studied the efficacy of indomethacin and ibuprofen given to larger premature infants (≤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 [5]. 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 [25]. Two studies increase the number of infants randomized and expand the information about the safety and efficacy of oral ibuprofen in more mature VLBW infants [26, 27]. We hope the same for our study.

Other recent studies support the notion that ibuprofen therapy is not devoid of renal effects in neonates [28,29,30]. Gournay et al.[30] noted an increase in creatinine in the prophylactic ibuprofen group and in those who received a second course of ibuprofen, which resolved in the second week of life. They also noted a decrease in urine output with ibuprofen as compared with placebo that returned to baseline after the first course. Ticker and Yildirim [28] described temporary oliguria and/or renal dysfunction after treatment with one course of ibuprofen that is similar to that seen with indomethacin. Vieux et al. [29] found a significant decrease in glomerular filtration and tubular function impairment in the ibuprofen group that was not seen in the patients who did not receive ibuprofen. But, similar to our study, renal failure has not been reported in any study using oral ibuprofen [19 – 24].

Rates of NEC reported with intravenous ibuprofen varied from 4.5% to 17% [19 – 24]. In a pool of 151 patients treated with oral ibuprofen, NEC was reported in12 (7.9%) cases. None of our patient had NEC or bowel irritation.

In published, randomized, clinical trials, no case of GEB was reported with intravenous ibuprofen. In a pool of 151 patients treated with oral ibuprofen, GEB was reported in 19 cases (12.6%). In our study, GEB developed in 3 patients in oral group and in no patient in intravenous group. The rate of IVH reported with intravenous ibuprofen in our study was similar to those reported previously [5,11,12,30].

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 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, but the differences were not statistically significant. The oral form was as safe as the intravenous form in terms of renal tolerance. A larger sample study is certainly needed for more definitive conclusion.

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