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Renal effects of ibuprofen during the treatment of patent ductus arteriosus in low birth weight premature infants

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Abstract

Background: Aim of this study was to assess the efficacy and safety of oral ibuprofen and intravenous ibuprofen for the early pharmacological treatment of patent ductus arteriosus (PDA) in preterm infants. *Methods:* A randomized, single-blinded, controlled study performed on premature neonates, 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. Serum creatinine (sCr), blood urea nitrogen (BUN) and urine output (UO) were recorded prior to start treatment, and after the course treatment. *Results:* 36 patients were treated with oral ibuprofen and 32 with intravenous ibuprofen in this period. After the first course 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). In the evaluation of renal tolerance, none of the patients had oliguria. The serum creatinine levels after the first and after the second treatment course did not differ significantly from the baseline for each group. *Conclusions:* Oral ibuprofen treatment seems to be as efficient as intravenous ibuprofen in closing PDA on the third day of life in low birth weight preterm infants and without significant changes of renal function.

Keywords

Ibuprofen, Patent Ductus Arteriosus, Renal Function, Serum Creatinine Level

1. Introduction

Patent ductus arteriosus (PDA) is common in very low birth weight (VLBW≤1500g) infants, and is associated with significant morbidities and mortality. Left-to-right shunting through the ductus may increase the risk of intraventricular hemorrhage (IVH) [2,3], necrotizing enterocolitis (NEC) [4], bronchopulmonary dysplasia, and death [5,6]. 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 [7,8]. However, indomethacin may lead to complications such as transient or permanent renal dysfunction [9,10], necrotizing enter colitis, and reduced cerebral oxygenation [11]. 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 [12]. 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 [1,6,17], ibuprofen, as is the case with other COX inhibitors, may not be exempt from causing some renal undesirable effects [18]. 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 [24]. In fact, any other pathological increase in vasoconstriction during the neonatal period, such as metabolic acidosis, asphyxia and thermic dysregulation, may slow down the maturation process and reduce renal perfusion [25]. Thus, the neonatal period is characterized by physiological processes with fast changes, which may profoundly affect the efficacy and safety of any drug therapy, especially because most of the drugs studied are eliminated through the kidney. The intravenous preparations of indomethacin and ibuprofen are available at exorbitant prices comparing with oral ibuprofen which is less expensive. Aim of this study was to assess the efficacy and safety of oral ibuprofen and intravenous ibuprofen for the early pharmacological treatment of PDA in preterm infants; to examine whether oral ibuprofen and venous ibuprofen treatment of PDA have comparable effects on renal function as evidenced by urine output, serum creatinine and plasma blood urea nitrogen.

2. Materials and Methods

The study was designed as a prospective, randomized, one blind, study. The study was conducted in the neonatal intensive care unit (NICU) 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.

The study enrolled preterm infants with a gestational age (GA) 28-32 weeks, birth weight ≤ 2000g, postnatal age 48-96 hours, and one of the following echocardiographic criteria: a duct size >1.5 mm; a left atrium-to-aorta ratio >1.4; left-to-right shunting of blood in addition to signs of PDA [30]. 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 (sCr) in excess of 1.6 mg/dl, blood urea nitrogen (BUN) 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) 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.

The 2 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).

2.1. Echocardiography

Color Doppler echocardiography (Vivid 3, sonde 7.5 Mhz) 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 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 a 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: sCr, BUN and urine output (UO), cranial ultrasonography, and echocardiography. All infants continued their current enteral feeding during the treatment. The success rate closure and evaluation of renal side efects were the major outcomes.

2.2. Statistical Analysis

We calculated that a study group of 68 patients would be appropriate 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%. SPSS for Windows (SPSS version 19.0.1, Chicago, IL), and Minitab (Minitab version 15.0, State College, PA) were used to conduct statistical data analyses. The data are presented as mean±standart deviation, frequency, or percentage. Paired-samples *t* test and independent–sample *t* test were used for continuous variables; the χ^2 was used for categorical variables. A p value of < 0.05 was considered significant. Chi-square analysis was performed to compare the proportion of patients experiencing the secondary outcomes of PDA closure.

3. Results

A total of 168 premature infants at gestational age <32 weeks and birth weight <2000g and SDR were admitted to our NICU, from January 2010 to December 2012 and underwent an echocardiografic Doppler ultrasound evaluation at the age of 48-96 hours. The entire study protocol was completed for 80 patients, with other cases excluded because of severe concomitant internal diseases, or when bleeding following the first ibuprofen administration was seen, and when the case had a fatal outcome. Baseline characteristics were similar between the two groups in the first 96 hours (Table 1). 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 (P=0.085). 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 needed surgical ligation.

Table 1. *Baseline Characteristics of the Study Patients*

Baseline characteristics	Oral ibuprofen (n. 36)	Intravenous ibuprofen (n. 32)	*P value*
Gestational age n. (%)			
28.1- 30 week	19 (52.7%)	18 (56.2%)	0.737
30.1- 32 week	17 (47.2%)	14 (43.7%)	0.713
Birthweight n. (%)			
≤1000g	9 (25%)	6 (18.7%)	0.340
1001- 1500g	15 (41.6%)	19 (59.3)	0.078
1501- 2000g	12 (33.3%)	7 (21.8%)	0.121
Gender n. (%)			
Male	22 (61.1%)	17 (53.1%)	0.454
Delivery by cesarean section n. (%)	20 (55.5%)	14 (43.7%)	0.236
Antenatal indometacine n. (%)	0	0	
Antenatal glucocorticoids n. (%)	26 (72.2%)	18 (56.2%)	0.157
Perinatal asphyxia n. (%)	11 (30.5%)	9 (28.1%)	0.754

Table 2. *Evaluation of renal function tests after first course of treatment*

Measurement	Oral ibuprofen (n. 36)			Intravenous ibuprofen (n. 32)		
	Before	*After*	*P value*	*Before*	*After*	*P value*
sCr (mg/dL)	1.10±0.25	1.07±0.23	0.608	1.08±0.22	1.085±0.24	0.929
BUN (mg/dL)	31.6±10.5	31.3±8.7	0.897	30.8±7.7	31.6±9.9	0.682
UO (mL/kg/h)	3.2± 1.0	2.8±0.8	0.071	3.08±0.85	3.3±0.5	0.192

Table 3. *Evaluation of renal function tests after second course of treatment*

Measurement	Oral ibuprofen (n. 6)			Intravenous ibuprofen (n. 9)		
	Before	*After*	*P value*	*Before*	*After*	*P value*
sCr (mg/dL)	1.07±0.24	1.09±0.24	0.877	1.20±0.95	0.97±0.45	0.598
BUN (mg/dL)	30.7±14.8	30.4±13.7	0.969	30.3±14.2	30.6±14.0	0.898
UO (mL/kg/h)	2.7±0.6	3.0±0.71	0.167	3.2±0.65	3.93±0.5	0.045

In the evaluation of renal tolerance, none of the patients had oliguria. The serum creatinine levels and blood urea nitrogen before and after the treatment did not differ significantly even for the oral ibuprofen group or intravenous ibuprofen group (Table 2). Renal function test results before and after the second course treatment did not differ significantly for each group treatment (Table 3).

4. Discussion

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. If oral ibuprofen is as efficient

as intravenous ibuprofen with no greater adverse effects, its simple administration and lower cost would be important advantages. 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 (71.8%) was similar to rates previously reported [1,6]. Some trials on the use of oral ibuprofen for closure of PDA have been recently published [27, 28, 29]. All studies had small sample sizes. Aly et al. [30] 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=0.75). Fakhraee et al. [31] 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>0.05). Efficacy of oral ibuprofen compared with intravenous indomethacin, was reported by Supapannachart et al. [32] and Chotigeat et al. [33] as well. In nonrandomized open trials, Heyman et al. [34] and Cherif et al. [27] reported a ductal closure with oral ibuprofen respectively in 21 (95.4%) of 22 patients and 38 (95%) of 40 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 [6]. 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 [35]. 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 [36, 37]. We hope the same for our study. Other recent studies support the notion that ibuprofen therapy is not devoid of renal effects in neonates [13,14,15]. Gournay *et al.* [15] 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 [13] 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.* [14] 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. Richards *et al.* [16] reported that the effectiveness of ibuprofen in closing a PDA decreased with a second course, and that creatinine was significantly higher in neonates receiving a second course as compared to controls. In fact, ibuprofen seems less potent over COX-1 [26], which is primarily involved in basal physiologic renal processes [20]. Renal adverse effects of ibuprofen seem to become disclosed when it is used with a prophylactic purpose. Such trials are characterized by an early administration, during the very first hours of life, as well as with a low gestational age of the enrolled patients [21,22]. As previously stated by Hammerman and Kaplan [23], the potential benefit achieved by prophylactic closing of a PDA does not justify exposing all infants to a drug that is not needed by as many as two-thirds of them, and which has potentially more serious side effects than the condition to which preventive efforts are aimed. But, similar to our study renal failure has not been reported in any study using oral ibuprofen.

However, renal alterations can still occur during ibuprofen treatment, although they may be transient, and consist of a reversible decrease in urine output or increase in serum creatinine concentration [19,25]. 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 [36,37], 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.

5. Conclusions

Our data indicate that, for preterm infants especially for VLBW infants, the rate of early ductal closure was comparable and the adverse effects did not differe statistically with oral ibuprofen in comparison to the intravenous route. The oral form was as safe as the intravenous form in terms of renal tolerance. Larger comparative studies are needed to validate these findings.

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