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TREATMENT STRATEGY OF PATENT DUCTUS ARTERIOSUS IN PRETERM INFANTS

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Objective – 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 was performed on premature neonates at the neonatal unit tertiary care hospital, from January 2010 to December 2012. The study enrolled 80 preterm infants with gestational age between 28-32 weeks, birth weight ≤ 2000 g, postnatal age 48-96 h, and with echocardiographically confirmed significant PDA (a duct size >1.5 mm). 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 (the first treatment course). Serum creatinine (sCr), blood urea nitrogen (BUN) and urine output (UO) were recorded prior to treatment, before each dose and after the first treatment course. **Results** – Forty patients were treated with oral ibuprofen and 40 with intravenous ibuprofen in this period. There was no difference between treatment groups in demographics or baseline renal function. After the first course of the treatment, the PDA closed in 28 (70%) of the patients assigned to the oral ibuprofen group, versus 23 (57.5%) of those enrolled in the intravenous ibuprofen group (p=0.35). In the evaluation of renal tolerance, none of the patients had oliguria. Moreover, in patients who underwent a second course of intravenous therapy, the urinary output significantly decreased, but the sCr levels after the first and after the second treatment course did not differ significantly from the baseline for each group. 7.5% of the intravenous group underwent surgery, versus 0% of the oral group. (p=0.23) **Conclusions** – Successful pharmacological closure of PDA can be achieved by the use of ibuprofen orally or intravenously, without statistically significant difference in efficacy and safety between the two treatments. Patients treated with ibuprofen intravenously probably have a much higher risk of undergoing surgery.

Key words: Patent ductus arteriosus ▪ Ibuprofen, Renal function ▪ Serum creatinine level ▪ Oliguria.

Introduction

Patent ductus arteriosus (PDA) is common in very low birth weight (VLBW ≤1500 g) infants, and is associated with significant morbidities and mortality. Left-to-right shunting through the ductus may increase the risk of intraventricular hemorrhage (IVH) (1, 2), necrotizing enterocolitis (NEC) (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), NEC, 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 (6, 12, 13), ibuprofen, as is the case with other COX inhibitors, may not be exempt from causing some renal undesirable effects (14).

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). In fact, any other pathological increases in vasoconstriction during the neonatal period, such as metabolic acidosis, asphyxia and thermic dysregulation also reduce renal perfusion (16). Thus, the neonatal period is characterized by physiological processes with rapid 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, compared with oral ibuprofen, which is less expensive.

Methods

The study was designed as a prospective, randomized, one blind, study. The adaptive biased-coin randomization method was used to generate the allocation sequence (Urn Randomization Program). The study was conducted in the neonatal intensive care unit (NICU) of the University Hospital for Obstetrics and Gynecology, Tirana, Albania, between January 2010 and December 2012, and was approved by the local ethics committee and by the scientist council of the University. The study enrolled preterm infants with a gestational age (GA) of 28-32 weeks, birth weight ≤ 2000 g, postnatal age 48-96 hours and RDS with significant PDA (30). Color Doppler echocardiography (Aloka, 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 we found a duct size >1.5 mm. GA was assessed by obstetrical dating criteria, or, when obstetrical data was inadequate, by Ballard examination (September 1991).

Exclusion criteria were major congenital abnormalities, right–to-left ductal shunting, life-threatening infection, grade 3 or 4 IVH, 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/mm3, clinical bleeding tendency as revealed by haematuria, blood in the gastric aspirate or in the stools, blood in the endo-

tracheal 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 either oral ibuprofen (Brufen, Abbot S.r.l, Italy Algofren), where 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), that was infused over a 15-minute period with a syringe pump. 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. 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. Cranial ultrasound was repeated 1 week after the last ibuprofen dose and again before discharge from the ward. Hematochemical analyses were performed 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.

The major outcome of the analysis was success rate closure of the PDA.

Secondary outcomes were: Renal side effects, assessed with measurement of sCr levels, BUN serum levels and UO and Mortality.

Statistical analysis

For sample size calculation, the power was set at 80%, a commonplace procedure in similar studies. The difference of 25% was anticipated in the degree of closure in the oral ibuprofen group of 95%. This assumption was based on similar reports from the international literature. The calculation revealed the sample size of 40 subjects in each arm. Paired-samples T-test was used for comparison of mean values between two related (dependent) groups. Chi-square test was used to compare independent proportions between categorical variables. A p value of <0.05 was considered significant. Random allocation sequence was generated using the Urn Randomization Program.

Results

A total of 168 premature infants with GA 28-32 weeks, birth weight <2000 g and RDS were admitted to our NICU, from January 2010 to December 2012 and underwent echocardiographic evaluation at the age of 48-96 hours. Ninety-four of them showed significant PDA. Fourteen infants were excluded for several reasons (see Fig. 1), and 80 infants were randomized to have oral ibuprofen or intravenous ibuprofen.

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 28 (70%) of the patients assigned to the oral ibuprofen group, versus 23 (57.5%) of those enrolled in the intravenous ibuprofen group (p=0.35). Six patients (15%) in the oral ibuprofen group required a second course of drug therapy, compared

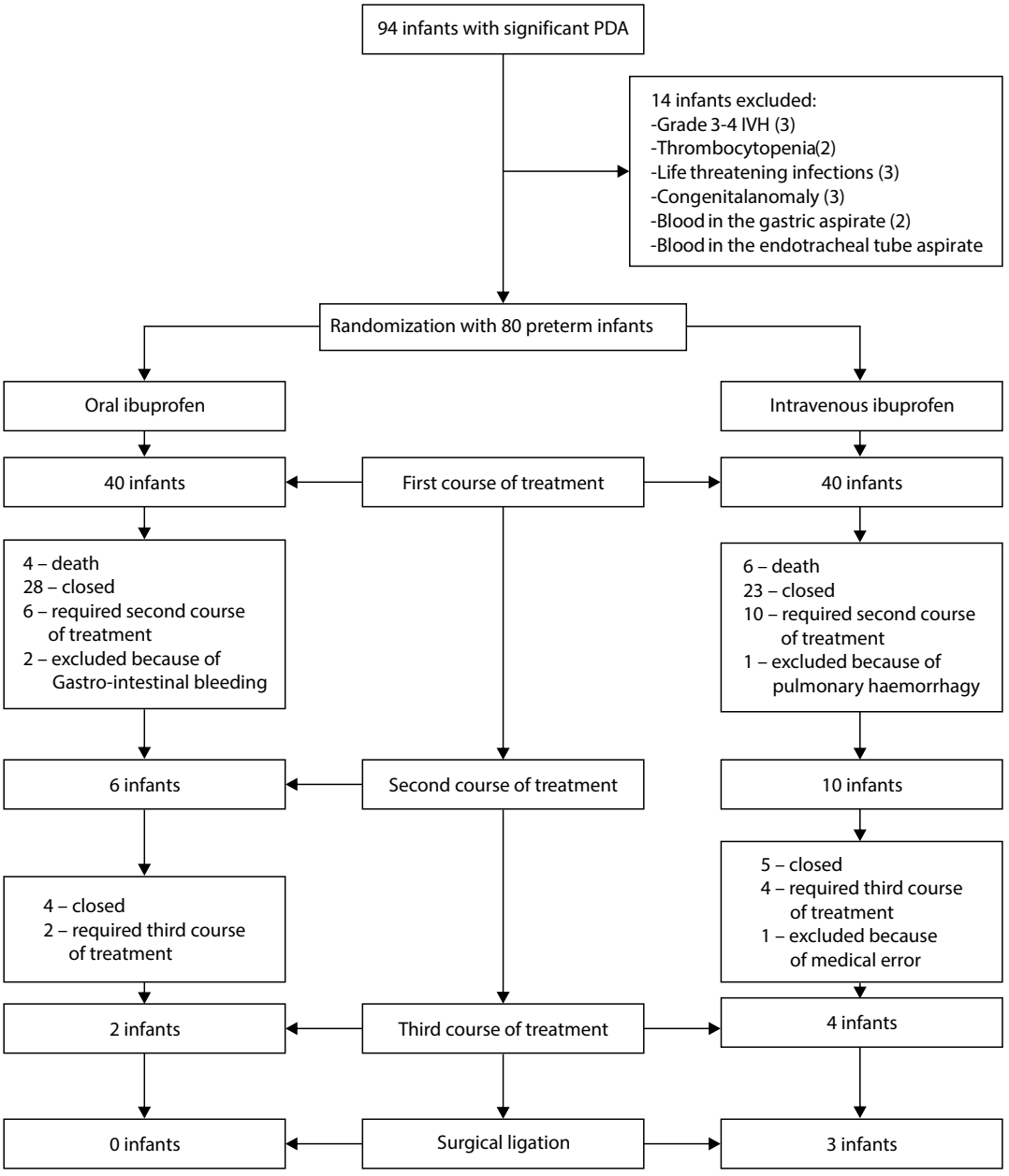

Fig. 1 *Flow chart of the two randomized group (oral and intravenous group).*

with 10 (25%) in the intravenous ibuprofen group (p=0.4). Two in the oral ibuprofen group (5%) required a third course of drug therapy, compared with 4 (10%) 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. Only three patients underwent surgical ligation (7.5%) in the intravenous ibuprofen versus 0 in the oral ibuprofen group (p=0.23).

Table 1 Baseline characteristics of the study patients

Characteristics	Oral ibuprofen (n=40)	Intravenous ibuprofen (n=40)
	n (%)	n (%)
Gestational age (week)		
28.1- 30	19 (47.5)	18 (45)
30.1- 32	21 (52.5)	22 (55)
Birthweight (g)		
≤1000	9 (22.5)	6 (15)
1001-1500	15 (37.5)	19 (47.5)
1501-2000	16 (40)	15 (37.5)
Male	22 (55)	17 (42.5)
Delivery by cesarian section	20 (50)	14 (35)
Antenatal indometacine	-	-
Antenatal glucocorticoids	26 (65)	18 (45)
Pulmonary hemorrhage	-	2 (5)
Gastro-intestinal bleeding	1 (2.5)	0
Perinatal asphyxia	11 (27.5)	9 (22.5)
Various reason (human error)	0	1 (2.5)

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

Measurement	Oral ibuprofen (n=36)*			Intravenous ibuprofen (n=34)*		
	Before	After	p	Before	After	p
sCr (mg/dl; M±SD)	1.10±0.25	1.07±0.23	0.608	1.08±0.22	1.085±0.24	0.929
BUN (mg/dl; M±SD)	31.6±10.5	31.3±8.7	0.897	30.8±7.7	31.6±9.9	0.682
UO (mg/dl; M±SD)	3.2±1.0	2.8±0.8	0.071	3.08±0.85	3.3±0.5	0.192

sCr=serum creatinine concentration; BUN=blood urea nitrogen; UO=urine output, M±SD=Mean ± Standard Deviation *After 1st course of treatment, 4 patients from the oral group and 6 from the intravenous group died, thus we evaluated renal function tests only for 36 patients in the oral group and 34 patients in the intravenous group.

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

Measurement	Oral ibuprofen (n=6)			Intravenous ibuprofen (n=9)*		
	Before	After	p	Before	After	p
sCr (mg/dl; M±SD)	1.07±0.24	1.09±0.24	0.877	1.20±0.95	0.97±0.45	0.598
BUN (mg/dl; M±SD)	30.7±14.8	30.4±13.7	0.969	30.3±14.2	30.6±14.0	0.898
UO (mg/dl; M±SD)	2.7±0.6	3.0±0.71	0.167	3.2±0.65	3.93±0.5	0.045

sCr=serum creatinine concentration; BUN=blood urea nitrogen; UO=urine output, M±SD=Mean±Standard Deviation. *The second course of treatment was undertaken for 6 patients in the oral group and 10 patients in the intravenous group, but given a medical error, one patient from the intravenous group was excluded from the evaluation of renal function tests after the second course of treatment.

In the evaluation of renal tolerance, none of the patients had oliguria. The sCr levels and blood urea nitrogen before and after the treatment did not differ significantly for either the oral ibuprofen group or intravenous ibuprofen group (Table 2).

Renal function test results before and after the second course of treatment did not differ significantly for each group treatment (Table 3). In patients who underwent a second course of intravenous therapy, the urinary output was significantly decreased.

The mortality rate was different between treatment groups, 4 patients (10%) died in the oral ibuprofen group and 6 patients (15%) died in the intravenous group (OR=0.63, 95% CI: 0.16-2.43; p=0.502).

Discussion

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 28 of our 40 (70%) study infants achieving a successful outcome. Patients treated with Ibuprofen by intravenous route probably have much higher risk of a second course of therapy according to our study where 15% versus 25% underwent a second course of therapy, (p=0.4).

The rate of closure in the group assigned to intravenous ibuprofen after the complete treatment (92.5%) was similar to rates previously reported by Van Overmeire and Lago (5, 12). Some trials on the use of oral ibuprofen for closure of PDA have been published recently (17, 18, 19). All studies had small sample sizes. Aly et al. (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. Fakhraee et al. (21) in a randomized study, reported that PDA was closed in all 18 premature infants (≤34 weeks) given oral ibuprofen and in 15 of 18 premature infants given oral indomethacin. The 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. (25) reported 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 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 (26).

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). The 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 (27, 28).

In our study, patients treated with ibuprofen by intravenous route probably have a much greater risk of undergoing surgery (7.5% versus 0, p=0.23). The same result was found by Cherif et al., (17) with the rate of closure of PDA marginally favorable in the oral ibuprofen group (84.3% vs 62.5%, p=0.04; 95% confidence interval: 0.99–1.84). Surgical ligation of the PDA was performed in 1 (3.1%) patient in the oral ibuprofen group O and in 4 (12.5%) patients in the intravenous group (p=0.25) (17).

Other recent studies support the notion that ibuprofen therapy is not devoid of renal effects in neonates (29, 30, 31). Renal function test results before and after the second course of treatment did not differ significantly for each group treatment in our study, but patients who underwent a second course of intravenous therapy, urinary output was significantly decreased.

Gournay noted an increase in creatinine in the prophylactic ibuprofen group and in those who received a second course of ibu-

profen, which resolved in the second week of life (31). They also noted a decrease in urine output, with ibuprofen as compared with a placebo, that returned to baseline after the first course. Ticker and Yildirim (29) described temporary oliguria and/or renal dysfunction after treatment with one course of ibuprofen that is similar to that seen with indomethacin. Vieux 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 (30). Richards 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 (32).

In fact, ibuprofen seems less potent over COX-1, which is primarily involved in basal physiologic renal processes (10, 33). 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 (26). As previously stated by Hammerman and Kaplan (34), 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 at which the preventive efforts are aimed. But, as in our study, renal failure has not been reported in any study using oral ibuprofen.

However, renal alterations may still occur during ibuprofen treatment, although they may be transient, and consist of a reversible decrease in UI or increase in sCr concentration (16, 33). Since the renal tolerability of ibuprofen for renal function in the neonate is a major argument in favour of its use in the treatment of PDA (27, 28), our study expands our information about the safety and efficacy of oral ibuprofen in more mature VLBW infants. sCr levels and uremia in our patients were within the 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.

The mortality rate in our study was higher in the intravenous group, 15% versus 10%, (p=0.5), this result is different from the results of Cherif et al., where the mortality rate was higher in the oral ibuprofen group: 28.1% in the oral group versus 25% in the intravenous group (17).

Limitations of study

There are several limitations to our study. This was an open-label, one-blind study. 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 was the first experience that we have with ibuprofen (oral or intravenous) for treatment of PDA in preterm infants.

Conclusion

No statistically significant difference in efficacy and safety between the two treatments could be confirmed. Patients treated with ibuprofen by intravenous group have probably a much greater risk of undergoing surgery.

Authors' contributions: Conception and design: EP, AH; Acquisition, analysis and interpretation of data: AH, IB, SB; Drafting the article: EP, AH; Revising it critically for important intellectual content: EP, IB.

Conflict of interest: The authors declare that they have no conflict of interest.

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