Volume 4, issue 10, 2015 ● e-ISSN: 1857-8187 ● p-ISSN: 1857-8179

Research Article

Therapeutic Effect and Safety of Early Treatment of Patent Ductus Arteriosus with Oral Ibuprofen in Preterm Infants

Healthcare

Keywords: DBA, preterm births, Ibuprofen, treatment of early/late, side effects, complication..

Hoxha (Qosja) Alketa Corresponding author		**Pediatrician – Neonatologist, Neonatology Service, UHOG "Koço Gliozheni" Tirana, Albania.**
Tushe Eduart		**Pediatrician – Neonatologist, Neonatology Service, UHOG "Koço Gliozheni" Tirana, Albania**
Moisiu Rubena		**Obst. and Gynecologist, Obst. and Gyn. Service, UHOG "K. Gliozheni", Tirana, Albania.**
Prifti Enkeleda		**Obst. and Gynecologist, Obst. and Gyn. Service, UHOG "K. Gliozheni", Tirana, Albania.**
Celami Rustem		**Obst. and Gynecologist, Obst. and Gyn. Service, UHOG "K. Gliozheni", Tirana, Albania.**
Pistulli Edmond		**Pediatrician, Pediartics Service, UHC "Mother Teresa", Tirana, Albania.**
Kuneshka Numila		**Pediatrician, Pediartics Service, UHC "Mother Teresa", Tirana, Albania.**

Abstract

Background: Patent ductus arteriosus (PDA) is a common problem encountered in premature infants, especially those with respiratory distress syndrome. PDA can lead to life-threatening complications. Intravenous ibuprofen was shown to be as effective and to cause fewer side effects. If ibuprofen is effective intravenously, it will probably be effective orally too. Aim: This study was designed to determine the effectiveness and safety of oral ibuprofen compared to IV ibuprofen or no intervention for closing a PDA in preterm infants with RDS. Material and methods: A prospective study, randomized, a blind fold was conducted in NICU, at UOGH "Koço Gliozheni", Tirana, from February 2010-August 2013. The study included a total of 128 preterm infants, 28-35weeks, ≤2500gr birth weight, in the first 48-96 hours of life, with SDR and confirm the presence of DBA's (Ø≥1.5mm) by echocardiografic examination. Infants were treated with Ibuprofen oral, intravenous Ibuprofen, no medical interventions, in randomized order. The cycle of treatment: 10 + 5 + 5/mg/kg, every 24 hours. Were highlighted the basic characteristics of infants included in the study, the effectiveness of treatment (closure of DBA's), side effects, complications, and the effectiveness of treatment.For continuous variables were calculated the average and standard deviation. p≤0.05 value was accepted as statistically significant. All tests are two-sided. RR and OR were presented with 95%CI. Results: 38 infants were treated with Ibuprofen oral, 35 infants with intravenous Ibuprofen and 37 infants underwent no medical intervention. The effectiveness of early treatment: DBA remained open, after early treatment, in 7foshnja (18.4%) in group oral Ibuprofen vs 20 infants (54%) in the group that did not undergo any medical intervention [RR = 0.34; 95% CI = 0.16-0.7; p = 0.04], vs 6 infants (17.1%) in the group of intravenous Ibuprofen [RR = 1.07; 95% CI = 0.4-2.8; p≥0.05]. There was observed no statistically significant change of direction of side effects and complications, p≥0.05. Conclusions: Oral Ibuprofen is an effective and safe alternative when used for the treatment of DBA's to babies born prematurely and with low birth weight.

Introduction

Patent ductus arteriosus (PDA) is a common problem encountered in premature infants, especially those with respiratory distress syndrome[1,2]. PDA is an open vascular channel between the lungs and the heart. It should close after birth, but sometimes remains open because of the baby's immature stage of development[3]. The incidence of patent ductus arteriosus (PDA) in preterm infants varies between 40% and 60% on the third day of life, depending on the estimated gestational age[4-6]. In healthy preterm infants of ≥30 weeks' gestation, duct closure occurs by the fourth day after birth, while preterm infants of <30 weeks' gestation, with severe respiratory distress, have a 65% incidence of PDA beyond the fourth day of life[7-9]. The open ductus produces hemodynamic problems, which can lead to numerous clinical complications including congestive heart failure, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and death. Epidemiological data showing associations between the presence of a PDA and some of the major complications of prematurity have strengthened the widely held belief that PDA is harmful[10]. Treatment options in the closure of PDA include pharmacological therapy and surgical ligation[11]. The exact population of preterm babies that benefit from PDA treatment is unknown. The current clinical approach to a patent ductus arteriosus (PDA) in the preterm infant is varied and controversial. Although some clinicians treat a PDA prophylactically, others treat a PDA when mild signs present within a few days after birth. Other clinicians take an ''expectant'' approach and allow for possible spontaneous closure, treating a PDA at a later time, only when signs indicate hemodynamic significance[12]. Indeed, among neonatologists in various institutions and even

within the same center, there are significant differences in the approach to treat a PDA as far as timing, duration, dosing schedule and choice of the COX inhibitors are concerned [13].

Intravenous indomethacin may lead to renal impairment, enterocolitis, and intraventricular hemorrhage. Intravenous ibuprofen was shown to be as effective and to cause fewer side effects. If ibuprofen is effective intravenously, it will probably be effective orally, too[14]. The procedure to purchase intravenous ibuprofen or indomethacin is administratively long and complex in Albania so to use oral ibuprofen when needed seems to be an alternative treatment for closing PDA. Although oral ibuprofen can be an easy-to-administer, cheap, and efficacious alternative for treating PDA, renal tolerance of dosing regimens may be critical and needs to be evaluated, especially in VLBW infants[14-20]. Three different approaches have been investigated including prophylactic treatment shortly after birth irrespective of the state of PDA, presymptomatic treatment using echocardiography at variable postnatal ages to select infants for treatment prior to the duct becoming clinically significant, and symptomatic treatment once PDA becomes clinically apparent or hemodynamically significant[21]. To date, there has been a lack of placebo-controlled data specific to the effectiveness or safety of early ibuprofen use (< 72 hours), but before a hemodynamically symptomatic PDA develops (3 to 9 days). Unfortunately, the delaying of therapy until hemodynamic symptoms of a persistent PDA appear, usually > 3 to 6 days, increases the likelihood of developing PDA-related morbidities and may decrease the success of pharmacological closure[22,23].
This study was designed to determine the effectiveness and safety of oral ibuprofen compared to IV ibuprofen or no intervention for closing a PDA in preterm infants with respiratory distress syndrome.

Materials and methods

This study was designed in December 2009 and began implementation in January 2010. It was designed as a prospective, randomized and single-blinded study because the cardiologist who performed the echocardiography was blind to the child's clinical condition and the treatment administered to the child. This study was conducted in the Neonatal Intensive Care Unit of the UHOG "Koço Gliozheni", Tirana, Albania, during a period of 43 months from February 10, 2010, to August 30, 2013. This study was approved by the Medicine University and Neonatology Departament.

Criteria for enrollment were: gestational age ≤ 35 weeks and a birthweight ≤ 2500 g[11,16-18,24-32], postnatal age between 48 and 96 hours, respiratory distress requiring more than 25% of oxygen supplementation, and echocardiographic evidence of left-to-right significant shunting PDA. We need to note that in this study will be presented only data from babies inborn at our maternity so this is an inclusion criterion to.

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, platelet count < 60,000/mm^3, clinical bleeding tendency (i.e., oozing from puncture sites), serum creatinine level > 140 mmol/L, serum urea nitrogen > 14 mmol/L, hiperbilirubinemia necessitating exchange transfusion, expected survival > 48 hours in the opinion of the attending neonatologist; approved by the medical director or study coordinator. The presence of one exclusion criterion was enough to exclude the patient from the study. GA was assessed by obstetrical dating criteria or, when obstetrical data was inadequate, by Ballard examination.

Study Design
There was no bias in patients recruitment. All infants who met the entry criteria were randomized into three groups to receive either (1) oral ibuprofen (Brufen, Abbot S.r.l, Italy Algofren) 10 mg/kg was diluted in 3 mL of saline solution then administered through a feeding tube followed by flushing with distilled water to ensure delivery of the drug, (2) 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 using umbilical venous catheter or peripheral IV site, or (3) no treatment. 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 (oral or IV) 5 mg/kg was administered, or no treatment. A

third equivalent dose was given after another 24 hours. If this therapy failed to promote ductal closure a second course with ibuprofen is performed. Hematochemical analyses were preformed daily in the unit during the first days of life. Cranial ultrasound examination was performed, first before entering the study, then repeated after each dose, 1 week after the last dose and before discharge. The study patients were assessed for IVH and for periventricular leukomalacia (PVL) which were graded, respectively according to classifications of Papille and of de Vries, with higher grades indicating greater severity[33,34].

Subgroup analysis

Infants in Group (1), (2) and (3) subdivided into three subgroups according to birth weight: ≤1500g; 1501-2000g; 2001-2500g and according to gestational age: 28-30w; 301/7-33w; 331/7-35w.

Color Doppler Echocardiography

Echocardiography was the gold standard technique used for diagnosis[35,36]. Color Doppler echocardiography (Vivid 3 sonde 7.5Mhz) was performed on all infants who met the inclusion criteria. Physicians performing echocardiography and making the decision for first-second- and third-dose administration were unaware of assignment. The purpose was to confirm the presence of a left-to-right ductal shunting, to evaluate its degree, and to measure the internal diameter of the ductus. 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. In each group, in case there was only minor ductal shunting (ductal size was < 1.0 mm) after therapy and the patient did not require respiratory support, no additional treatment of the ductus was attempted. 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.

Concomitant treatment

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 five days if blood cultures were negative. Dopamine infusion at the dose of 3 μg/kg per minute was started once urine output deer ≤1 mL/kg per hour. All infants continued their current enteral feeding during the treatment.

Primary and secondary outcome

Primary outcomes were related to effectiveness. The success rate which was defined as closed duct on control echocardiography after the completed first treatment course in preterm infants with respiratory distress were the major outcomes of the study. Secondary outcomes were related to safety: renal failure, anemia, pneumothorax, pulmonary haemorrhage, chronic lung disease (CLD), intraventricular haemorrhage (grades I–IV), LPV, necrotising enterocolitis (NEC), BDP, intestinal perforation, gastrointestinal bleeding, definite sepsis (clinical symptoms and signs of sepsis and a positive blood bacterial culture) and death.

Statistical analysis

Statistical analysis of data was performed using the Chi-square test, the Mann Whitney U test, or Fisher's exact test. Relative risk and 95% confidence intervals were estimated by Poisson regression with robust error variance. Continuous data, such as weight, gestational age, serum blood urea nitrogen and Cr levels, and urine output are presented as mean ± standard deviation. A p value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed on a personal computer with the statistical package SPSS for Windows (Version 18.0, SPSS, Chicago, IL, USA).

Results

During the period of February 2010 to August 2013, a total of 431 preterm infants admitted in our NICU and fulfilled entry study criteria. This unit serves as a referral Level III NICU in our country but we decided to present in this study data only from inborn infants. They had Doppler-ultrasonographic and 145 (33%) of them had evidence of PDA (ducutal diameter ≥ 1.5mm). 17 infants were excluded for different reasons. A total of 128 infants were randomly assigned to received oral ibuprofen (n.44), IV ibuprofen (n.40) and no treatment (n.44) (Fig.1). The baseline characteristics were similar between three groups of infants and were no significant differences, $p > 0.05$(Tab.1 and Tab.2). Six infants in oral ibuprofen group, five infants in IV ibuprofen group and seven infants in no treatment group interrupted treatment for different reasons (Fig.1).

.

Figure 1. Infants enrolled in the study protocol

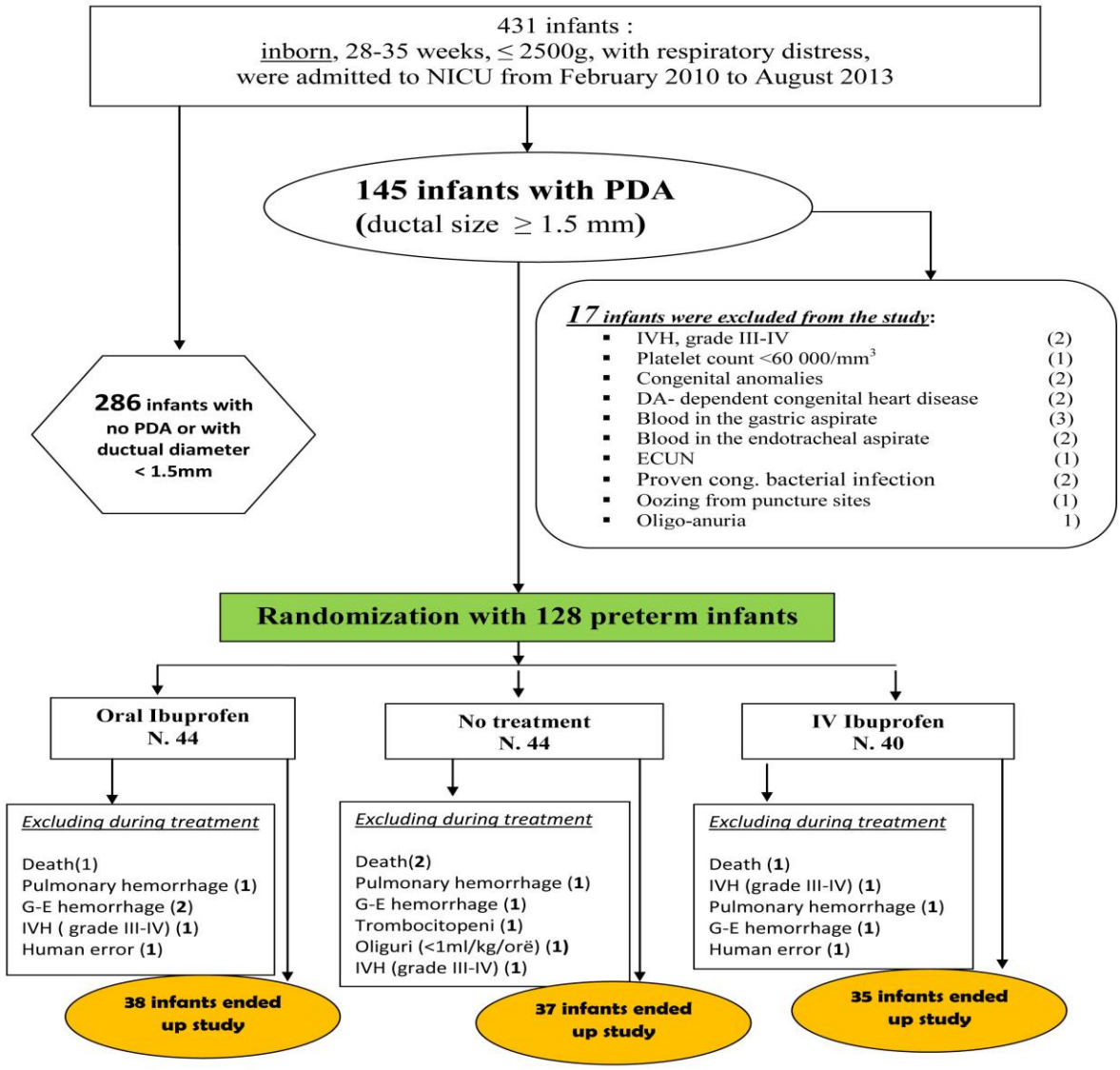

Table 1.
Demographic data of both groups, oral ibuprofen/no treatment

	Oral Ibuprofen N. 44		No treatment N.44		p value
Gestational age (week) (n, %)					
28 – 30 w	10	*22%*	9	*20.4%*	0.63
30 e 1/7 - 33 w	20	*45.4%*	21	*47.7%*	0.86
33 e 1/7 – 35 w	14	*31.8%*	14	*31.8%*	0.68
Birth weight (g) (n, %)					
≤1500g	17	*38.6%*	19	*43.1%*	0.94
1501-2000g	11	*25%*	13	*29.5%*	0.83
2001-2500g	16	*36.3%*	12	*27.2%*	0.91
Gender (n, %)					
F	24	*54.5%*	26	*59%*	0.97
M	20	*45.4%*	18	*40.9%*	0.96
Caesarean delivery (n, %)	18	*40.9%*	19	*43.1%*	0.84
Prenatal steroids (n, %)	12	*27.2%*	14	*31.8%*	0.86
Perinatal asphyxia (n, %)	13	*29.5%*	12	*27.2%*	0.75
Presence of early onset sepsis (n, %)	9	*20.4%*	11	*25%*	0.77

Table 2 *Demographic data of both groups, oral ibuprofen/IV ibuprofen*

	Oral Ibuprofen N.44		IV Ibuprofen N.40		p value
Gestational age (week) (n, %)					
28 – 30 w	10	*22%*	11	*27.5%*	0.83
30 e 1/7 - 33 w	20	*45.4%*	18	*45%*	0.76
33 e 1/7 – 35 w	14	*31.8%*	11	*27.5%*	0.83
Birth weight (g) (n, %)					
≤1500g	17	*38.6%*	17	*42.5%*	0.90
1501-2000g	11	*25%*	11	*27.5%*	0.72
2001-2500g	16	*36.3%*	12	*30%*	0.95
Gender (n, %)					
F	24	*54.5%*	22	*55%*	0.79
M	20	*45.4%*	18	*45%*	0.76
Caesarean delivery (n, %)	18	*40.9%*	18	*45%*	0.92
Prenatal steroids (n, %)	12	*27.2%*	10	*25%*	0.71
Perinatal asphyxia (n, %)	13	*29.5%*	11	*27.5%*	0.72
Presence of early onset sepsis (n, %)	9	*20.4%*	8	*20%*	0.55

We had a minimum value of PDA of 1.5 mm (as inclusion criteria) and a maximum of 3.4 mm (average 2.2mm; standard deviation ±0.6mm) for all infants included in the study.

Efficacy of Treatment

The effectiveness of early treatment: DBA remained open, after early treatment (first course), in 7 infants (18.4%) in group oral Ibuprofen versus 20 infants (54%) in the group that did not undergo any medical intervention [RR = 0.34; 95% CI = 0.16-0.7; p = 0.04], versus 6 infants (17.1%) in the group of intravenous Ibuprofen [RR = 1.07; 95% CI = 0.4-2.8; p≥0.05]. The subgroup analysis revealed that: oral ibuprofen treatment was more effective versus no treatment at closing PDA in patients with birth weight ≤ 1500g or in patients with gestational age 28-30w and 30 e 1/7-33w, there were no significant differences in the rate of closure between the two groups oral ibuprofen versus IV ibuprofen (Tab. 3, 4). All infants, in the oral and IV Ibuprofen groups, who received second course of treatment reached closure of PDA. There was no reopening of the ductus after closure was achieved.

Seventeen infants from no treatment group reached spontaneous closure and 20 of them came under "late or expectant therapy" [4,5,12,37,45] but the outcome of this infants is not objective of this study. Nine infants in the oral ibuprofen group and 13 infants in IV ibuprofen group were treated with 1 dose of ibuprofen, 5 infants in the oral ibuprofen group and 5 infants in IV ibuprofen group were treated with 2 doses of ibuprofen and 24 infants in the oral ibuprofen group and 17 infants in IV ibuprofen group were treated with 3 doses of ibuprofen.

Table 3. *Comparison between failure to close the PDA: oral ibuprofen/IV ibuprofen*

Variable	Oral Ibuprofen N.38		IV Ibuprofen N.35		p value	Relative risk (95% confidence interval)	
Birth weight (n,%)							
≤1500g	3	*23%*	3	*21.4%*	0.9	1.1	0.26-4.41
1501-2000g	2	*20%*	2	*20%*	1.0	1.0	0.17-5.77
2001-2500g	2	*13.3%*	1	*9%*	0.7	1.4	0.15-14.2
Gestational age (n,%)							
28-30w	2	*25%*	3	*37.5%*	0.6	0.6	0.14-2.97
30 e 1/7 - 33 w	3	*16.6%*	2	*12.5%*	0.7	1.3	0.25-6.99
33 e 1/7 – 35 w	2	*16.6%*	1	*9%*	0.6	1.8	0.19-17.5

Table 4. *Comparison between failure to close the PDA: oral ibuprofen/no treatment*

Variable	Oral Ibuprofen N.38		No treatment N.37		p value	Relative risk (95% confidence interval)	
Birth weight (n,%)							
≤1500g	3	*23%*	10	66.6*%*	0.04*	0.3	0.12-0.9
1501-2000g	2	*20%*	8	72.7*%*	0.05	0.3	0.07-0.98
2001-2500g	2	*13.3%*	2	18.1*%*	0.7	0.7	0.12-4.43
Gestational age (n,%)							
28-30w	2	*25%*	7	87.5*%*	0.04*	0.3	0.08-0.97
30 e 1/7 - 33 w	3	*16.6%*	11	64.7*%*	0.01*	0.2	0.08-0.76
33 e 1/7 – 35 w	2	*16.6%*	2	16.6*%*	1.0	1.0	0.16-5.98

Safety outcomes and adverse events

In the evaluation of renal tolerance, none of the patients had oliguria. Comparison of levels of serum creatinine and blood urea nitrogen before and after treatment did not differ significantly for either the oral ibuprofen, the IV ibuprofen and the no treatment group (Tab. 5).

Table 5. *Evaluation of renal function test before and after first course of treatment*

	Oral Ibuprofen group (n. 38)			IV Ibuprofen group (n. 35)			No treatment group (n.37)		
Measurement	Before	After	p	Before	After	p	Before	After	p
sCr (mg/dl; M±SD)	1.10±0.25	1.07±0.23	0.60	1.08±0.22	1.08±0.24	0.92	1.20±0.95	0.97±0.45	0.59
BUN (mg/dl; M±SD)	31.6±10.5	31.3±8.7	0.89	30.8±7.7	31.6±9.9	0.68	30.3±14.2	30.6±14.0	0.89
UO (mg/dl; M±SD)	3.2±1.0	2.8±0.8	0.07	3.08±0.85	3.3±0.5	0.19	2.7±0.6	3.0±0.71	0.16

sCr = serum creatinine concentration; BUN = blood urea nitrogen; UO = urine output. M±SD = Mean ± Standard Deviation.

Table 6. *Safety outcomes and adverse events related to birth weight*

	Oral ibuprofen group (n. 44)			IV ibuprofen group (n.40)			No treatment group (n. 44)		
Birth weight (n, %)	≤ 1500g	1501 -2000g	2001 -2500g	≤ 1500g	1501 -2000g	2001-2500g	≤ 1500g	1501-2000g	2001 - 2500g
Mortality	**4** *(23%)*	**0***(0%)*	**0***(0%)*	**4***(23%)*	**0***(0%)*	**1***(8%)*	**3***(16%)*	**0***(0%)*	**0***(0%)*
IVH (grade III-IV)	**2** *(12%)*	**1***(9%)*	**0***(0%)*	**1***(5.8%)*	**1***(9%)*	**1***(8%)*	**1***(5%)*	**1***(8%)*	**1***(8%)*
PVL	**1***(5.8%)*	**0***(0%)*	**0***(0%)*	**1***(5.8%)*	**0***(0%)*	**0***(0%)*	**1***(5%)*	**1***(8%)*	**0***(0%)*
Trombocitopenia <60 000/ mm^3	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**1***(5%)*	**0***(0%)*	**0***(0%)*
NEC	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*
BPD	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*
Anemia(need transfusion)	**4***(23%)*	**2***(18%)*	**1***(6.2%)*	**3***(17%)*	**2***(18%)*	**1***(8%)*	**5***(26%)*	**2***(15%)*	**1***(8%)*
Pneumothorax	**1***(5.8%)*	**0***(0%)*	**0***(0%)*	**2***(12%)*	**0***(0%)*	**0***(0%)*	**2***(10%)*	**0***(0%)*	**0***(0%)*
Pulmonary haemorrhage	**2***(12%)*	**2***(18%)*	**0***(0%)*	**2***(12%)*	**1***(9%)*	**0***(0%)*	**3***(16%)*	**2***(15%)*	**0***(0%)*
Chronic lung disease	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*
Intestinal perforation	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*
G-E bleeding	**4***(23%)*	**2***(18%)*	**0***(0%)*	**2***(12%)*	**1***(9%)*	**0***(0%)*	**5***(26%)*	**2***(15%)*	**1***(8%)*

Table 7. *Safety outcomes and adverse events related to postnatal age*

	Oral ibuprofen group (n. 44)			IV ibuprofen group (n.40)			No treatment group (n. 44)		
Gestational age (n, %)	28-30w	30e1/7-33w	33 e1/7 -35w	28-30w	30e1/7-33w	33 e1/7 -35w	28-30w	30e1/7-33w	33 e1/7 -35w
Mortality	**3***(30%)*	**1***(5%)*	**0***(0%)*	**3***(27%)*	**1***(5.5%)*	**1***(9%)*	**3***(30%)*	**0***(0%)*	**0***(0%)*
IVH (grade III-IV)	**2***(20%)*	**1***(5%)*	**0***(0%)*	**1***(9%)*	**1***(5.5%)*	**1***(9%)*	**1***(11%)*	**1***(5%)*	**1***(7%)*
PVL	**1***(10%)*	**0***(0%)*	**0***(0%)*	**1***(9%)*	**0***(0%)*	**0***(0%)*	**1***(11%)*	**1***(5%)*	**0***(0%)*
Trombocitopenia <60 000/ mm^3	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**1***(11%)*	**0***(0%)*	**0***(0%)*
NEC	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*
BPD	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*
Anemia(need transfusion)	**3***(30%)*	**4***(20%)*	**0***(0%)*	**4***(36%)*	**2***(11%)*	**0***(0%)*	**4***(44%)*	**4***(19%)*	**0***(0%)*
Pneumothorax	**1***(10%)*	**0***(0%)*	**0***(0%)*	**2***(18%)*	**0***(0%)*	**0***(0%)*	**2***(22%)*	**0***(0%)*	**0***(0%)*
Pulmonary haemorrhage	**3***(30%)*	**1***(5%)*	**0***(0%)*	**2***(18%)*	**1***(5.5%)*	**0***(0%)*	**3***(30%)*	**2***(10%)*	**0***(0%)*
Chronic lung disease	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*
Intestinal perforation	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*	**0***(0%)*
G-E bleeding	**3***(30%)*	**3***(15%)*	**0***(0%)*	**2***(18%)*	**1***(5.5%)*	**0***(0%)*	**3***(30%)*	**3***(14%)*	**1***(7%)*

NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; BPD, bronchopulmonary dysplasia; PVL, periventricular leukomalacia.

Safety endpoints have been summarized in Table 6, 7. With respect to complications and adverse events, there were no differences in the proportion of infants related to mortality, IHV (grade III-IV), PVL, Trombocitopenia<60 000/ mm^3, Anemia (need transfusion), Pneumothorax , Pulmonary haemorrhage , G-E bleeding between three groups. No infant had intestinal perforation, NEC, BDP, CLD and hiperbilirubinemia necessitating exchange transfusion.

Discussion

Given the reduction in the side effects noted in meta-analysis, ibuprofen currently appears to be the drug of choice[11]. However, the unavailability of intravenous ibuprofen in certain regions of world and the availability of inexpensive oral preparations have led to the nasogastric administration of oral ibuprofen in preterm infants with PDA. About 29% of NICUs in Europe reported the use of oral ibuprofen for ductal closure[43]. The purpose of this study was to evaluate the effectiveness and safety of early closure of nonsymptomatic PDA within 72 hours of birth in LBW infants with evidence of ductal shunting by echocardiogram and presence of RDS with oral ibuprofen. In contrast to other ibuprofen studies this study was unique in its design. This is the first randomized study, to our knowledge, comparing oral ibuprofen, intravenous ibuprofen and no treatment in closure of PDA in preterm infants with RDS.

This study was designed to answer questions from some practitioners who believe spontaneous closure will occur and will wait on active treatment until clinical symptoms present. No treatment group was used for comparison to address the specific question: does ibuprofen reduce the need for rescue therapy by early recognition and treatment of an asymptomatic, but early identifiable PDA[38], but like other studies [38,45, 46] we didn't use placebo because this was not a blind study. We used no treatment group to evaluate the safety of oral ibuprofen and to highlight the rate of spontaneous closure of PDA in preterm infants with RDS between 48-96 hours of life. For the first time (2008) we had the opportunity to have evidence of ductal shunting by echocardiogram in our NICU. Results from our study indicate that, in this preterm population, spontaneous closure rates were ~ 38%. In his article on the natural history of persistent DA, Campbell astutely predicted in 1968 that "as the years pass, more physicians will be advising operation for a persistent ductus arteriosus with no personal experience of its natural course without operation[43]. Results from Aranda's trial indicate that, in this ELBW population, spontaneous closure rates were no ≤30%, but the causative factors associated with pPDA and the natural history of DA closure in this high-risk population are poorly understood[9].

The treatment group (oral ibuprofen) showed a significantly higher closure rate of ductus arterious than the control group (no treatment group) after one course of treatment (81.6% vs 46%; [RR = 0.34; 95% CI = 0.16-0.7; p = 0.04]. Lin et al. showed a significantly higher closure rate of ductus arterious in treatment group than the control group after one course of treatment (84% vs 41%; P<0.01)[47]. Aranda et al.[38] showed a significant difference in the number of infants who had a completely closed ductus in the ibuprofen group versus placebo by study day 14 (69% versus 33%, $p = 0.046$), indicating that early therapy with ibuprofen versus placebo produces a meaningful clinical benefit in the treatment of a medically identifiable, but asymptomatic PDA. There was no difference in morbidities and mortality rate potentially associated with oral Ibuprofen treatment between patients receiving ibuprofen oral or patients in no treatment group (p>0.05), the same showed and other studies[38,46, 47].

If oral ibuprofen were proved to be as efficient as intravenous ibuprofen with no greater adverse effects, then its simple administration and lower cost would be important advantages. The treatment group (oral ibuprofen) showed the same efficacy for closure rate of ductus arterious as the IV ibuprofen after one course of treatment (81.6% vs 82.9%; [RR = 1.07; 95% CI = 0.4-2.8; p≥0.05].There was no difference in morbidities and mortality rate potentially associated with oral Ibuprofen treatment between patients receiving ibuprofen oral or patients receiving IV ibuprofen (p>0.05). Our study confirms the findings or prior trials, revealing comparable effectiveness of oral ibuprofen in closing PDA in preterm infants and also adds information pertaining to the renal safety of oral Ibuprofen treatment [11,16-18,24-32]. The authors concluded that oral ibuprofen might constitute a feasible alternative in the treatment of PDA. Indeed, in our study, the adverse effects were significantly fewer when the closure was achieved after an incomplete course of treatment.

Closure of the ductus, in our study, was obtained after 1 or 2 doses of treatment, in 85% of both groups. In our study, ibuprofen plasma levels were not measured.

Conclusions

Oral ibuprofen seems to be a safe alternative for the closure of PDA in LBW preterm infant. Our data indicate that, for preterm 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. On the other hand, our data suggest that ductal closure may be obtained with incomplete course of ibuprofen. Early closure of nonsymptomatic PDA within 72 hours of birth in preterm infants, the treatment of echocardiogram-confirmed but asymptomatic PDA with oral ibuprofen can significantly decrease the need for further pharmacological or surgical intervention as compared with no treatment.

Study limitations

Our study had few limitations. A limitation of our study is that it was no blind. The physicians and nurses were aware of the nature of the study. This allowed for some variability in treatment approaches by attending neonatologists; however, all clinicians used the same dosage regimen of PDA therapy and had similar approaches to PDA diagnosis. However, the most important outcome – PDA closure or not – was made by a cardiologist who was blinded to the treatment groups. Second, ELBW infants were not participants in our study.

The authors have declared that no competing interests exist.

Human Ethics

Consent was obtained by all participants in this study

Animal Ethics

Animal subjects: *This study did not involve animal subjects or tissue*

References

1. Hammerman C. Patent ductus arteriosus. *Clin Perinatol 1995*;22:457–477
2. Krueger E, Mellander M, Bratton D, Cotton R. Prevention of symptomatic patent ductus arteriosus with a single dose of indomethacin. *J Pediatr 1987*;111:749–754
3. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm and low birth weight (or both) infants (Review). *Cochrane Database Syst Rev2015;2:*CD003481.
4. Evans N. Preterm patent ductus arteriosus: should we treat it? *Journal of Paediatrics and Child Health*. 2012;48(9):753–758.
5. Clyman RI, Couto J, Murphy GM. Patent ductus arteriosus: are current neonatal treatment options better or worse than no treatment at all? *Seminars in Perinatology*. 2012;36(2):123–129.
6. Schena F, Ciarmoli E, Mosca F. Patent ductus arteriosus: wait and see? *Journal of Maternal-Fetal and Neonatal Medicine*. 2011;24(supplement 3):2–4.
7. Van Overmeire B, Chemtob S (2005) The pharmacologic closure of the patent ductus arteriosus. *Semin Fetal Neonatal Med* 10: 177-184.
8. S. L. Nemerofsky, E. Parravicini, D. Bateman, C. Kleinman, R. A. Polin, and J. M. Lorenz, "The ductus arteriosus rarely requires treatment in infants > 1000 grams," *American Journal of Perinatology*, vol. 25, no. 10, pp. 661–666, 2008.
9. J. Koch, G. Hensley, L. Roy, S. Brown, C. Ramaciotti, and C. R. Rosenfeld, "Prevalence of spontaneous closure of the ductus arteriosus in neonates at a birth weight of 1000 grams or less," *Pediatrics*, vol. 117, no. 4, pp. 1113–1121, 2006.
10. S Noori. Review. Patent ductus arteriosus in the preterm infant: to treat or not to treat? *Journal of Perinatology* (2010) 30, S31–S37
11. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants.*Cochrane Database Syst Rev2010;4:*CD003481.
12. Ilene R. S. Sosenko, M. Florencia Fajardo, Eduardo Bancalari. Timing of Patent Ductus Arteriosus Treatment and Respiratory Outcome in Premature Infants: A Double-Blind Randomized Controlled Trial. *J Pediatr 2012*.
13. Noori S, Seri I. Treatment of the patent ductus arteriosus: when, how and for how long?

J Pediatr 2009; 155: 774–776.
14. Cherif A, Jabnoun S, Khrouf N. Oral ibuprofen in early curative closure of patent ductus arteriosus in very premature infants. *Am J Perinatol 2007;*24:339–45.
15. Heyman E, Morag I, Batash D, et al. Closure of patent ductus arteriosus with oral ibuprofen suspension in premature newborns: a pilot study. *Pediatrics 2003;*112:e354.
16. Aly H, Lotfy W, Badrawi N, et al. Oral Ibuprofen and ductus arteriosus in premature infants: a randomized pilot study. *Am J Perinatol 2007;*24:267–70.
17. Lee SJ, Kim JY, Park EA, et al. The pharmacological treatment of patent ductus arteriosus in premature infants with respiratory distress syndrome: oral ibuprofen vs. indomethacin. *Korean J Pediatr 2008;* 9:956–63.
18. Cherif A, Khrouf N, Jabnoun S, et al. Randomized pilot study comparing oral ibuprofen with intravenous ibuprofen in very low birth weight infants with patent ductus arteriosus. *Pediatrics 2008;*122:e1256–61.
19. Erdeve O, Gokmen T, Altug N, et al. Oral versus intravenous ibuprofen: which is better in closure of patent ductus arteriosus? *Pediatrics 2009;*123:e763.
20. Gokmen T, Erdeve O, Altug N, et al. Efficacy and safety of oral versus intravenous ibuprofen in very low birth weight preterm infants with patent ductus arteriosus. *J Pediatr 2011;*158:549–554.e1.
21. Hesham Abdel-Hady, Nehad Nasef. Patent Ductus Arteriosus in Preterm Infants: Do We Have the Right Answers? *Biomed Res Int. 2013*; 2013: 676192.
22. Van Overmeire B, Smets K, Lecoutere D et al.. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. *N Engl J Med 2000*; 343: 674-681
23. Fanaroff A A, Stoll B J, Wright L L et al.. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Obstet Gynecol 2007*; 196: 147.e1-e8
24. Hariprasad P, Sundarrajan V, Srimathy G, Suthagar B, Ramadevi BS. Oral ibuprofen for closure of hemodynamically significant PDA in premature neonates. *Indian Pediatr 2002*; 39:99–100.
25. Supapannachart S, Limrungsikul A, Khowsathit P. Oral ibuprofen and indomethacin for treatment of patent ductus arteriosus in premature infants: a randomized trial at Ramathibodi Hospital. *J Med Assoc Thai 2002*;85(Suppl 4): S1252–S1258.
26. Chotigeat U, Jirapapa K, Layangkool T. A comparison of oral ibuprofen and intravenous indomethacin for closure of patent ductus arteriosus in preterm infants. *JMed Assoc Thai 2003*;86(Suppl 3):S563–S569.
27. S. Rajaei, N. M. Noori Oral Ibuprofen for Closure of Hemodynamically Significant Patent Dultus Arteriosus in Premature Neonates: a Pilot Study. *Iranian Heart Journal 2006*; 7 (2):15-18.
28. Fakhraee SH, Badiee Z, Mojtahedzadeh S, Kazemian M, Kelishad R. Comparison of oral ibuprofen and indomethacin therapy for patent ductus arteriosus in preterm infants. *Zhongguo Dang Dai Er Ke Za Zhi. 2007*;9(5):399–403.
29. Sh. Pourarian, N. Pishva, A. Madan, M. Rastegari Comparison of oral ibuprofen and indomethacin on closure of patent ductus arteriosus in preterm infants. *Eastern Mediterranean Health Journal*, Vol. 14, No. 2, 2008.
30. Akisu M, Ozyurek AR, Dorak C, Parlar A, Kultursay N. Enteral ibuprofen versus indomethacin in the treatment of patent ductus arteriosus in preterm new born infants. *Cocuk Sagligi ve Hastaliklari Dergisi 2001;*44:56-60.
31. Khashashneh and W. Amayreh. Ibuprofen oral suspension for the treatment of patent ductus arteriosus, *Middle East Journal of Family Medicine 7 (2009)*, 10–12.
32. H. Salama, A. Alsisi, H. Al-Rifai, et al., A randomized controlled trial on the use of oral ibuprofen to close patent ductus arteriosus in premature infants, *Journal of Neonatal-Perinatal Medicine 1 (2008)*, 153–158.
33. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm.*J Pediatr 1978*;92:529–534.
34. de Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. Behav Brain Res 1992;49:1–6.
35. El Hajjar M, Vaksmann G, Rakza T, et al. Severity of the ductal shunt: a comparison of different markers. *Arch Dis Child Fetal Neonatal Ed 2005*;90:F419–22.
36. Lai W W , Geva T, Shirali GS, et al. Guidelines and standards for performance of a pediatric echocardiogram: a report from the Task Force of the Pediatric Council of the American Society of Echocardiography. *J Am Soc Echocardiogr 2006*;19:1413–30.

37. Patrick J McNamara, Arvind Sehgal. Towards rational management of the patent ductus arteriosus: the need for disease staging. *Arch Dis Child Fetal Neonatal Ed 2007*;92:6 F424-F427
38. Aranda JV, Clyman R, Cox B, Van Overmeire B, Wozniak P, Sosenko I, et al. A randomized, double-blind, placebocontrolled trial of intravenous ibuprofen L-lysine for the early closure of non-symptomatic patent ductus arteriosus within 72 hours of birth in extremely low-birth-weight infants. *American Journal of Perinatology 2009*;26(3):235–45.
39. Tiker F, Yildirim SV: Acute renal impairment after oral ibuprofen for medical closure of patent ductus arteriosus. *Indian Pediatr* 2007, 44(1):54–5.
40. Gournay V, Roze JC, Kuster A, Daoud P, Cambonie G, Hascoet JM, Chamboux C, Blanc T, Fichtner C, Savagner C, Gouyon JB, Flurin V, Thiriez G: Prophylactic ibuprofen versus placebo in very premature infants: a randomised, double-blind, placebo-controlled trial. *Lancet* 2004, 364(9449):1939–44.
41. Richards J, Johnson A, Fox G, Campbell M: A second course of ibuprofen is effective in the closure of a clinically significant PDA in ELBW infants. *Pediatrics* 2009, 124(2):e287–e293.
42. Guimarães H, Rocha G, Tomé T, *et al.* Non-steroid anti-infl ammatory drugs in the treatment of patent ductus arteriosus in European newborns. *J Matern Fetal Neonatal Med* 2009;22 (Suppl 3):77–80.
43. Campbell M. Natural history of persistent ductus arteriosus. *Br Heart J*. 1968;30(1):4 –13.
44. Erdeve O, Yurttutan S, Altug N, Ozdemir R, Gokmen T, Dilmen U, et al. Oral versus intravenous ibuprofen for patent ductus arteriosus closure: a randomised controlled trial in extremely low birthweight infants. *Archives of Diseases in Childhood. Fetal and Neonatal Edition* 2012;97(4):F279–83.
45. Sosenko IR, Fajardo MF, Claure N, Bancalari E. Timing of patent ductus arteriosus treatment and respiratory outcome in premature infants: a double-blind randomized controlled trial. *Journal of Pediatrics* 2012;160(6):929–35.
46. Bagnoli F, Rossetti A, Messina G, Mori A, Casucci M, Tomasini B. Treatment of patent ductus arteriosus (PDA) using ibuprofen: renal side-effects in VLBW and ELBW newborns. *Journal of Maternal-Fetal & Neonatal Medicine* 2013;26(4):423–9.
47. Lin XZ, Chen HQ, Zheng Z, Li YD, Lai JD, Huang LH. Therapeutic effect of early administration of oral ibuprofen in very low birth weight infants with patent ductus arteriosus. *Chinese Journal of Contemporary Pediatrics* 2012;14(7):502–5.