Is the prophylaxis of patent ductus arteriosus useful in extremely premature infants?

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SUMMARY: Bersani I, De Carolis MP, Lacerenza S, De Rosa G, Fusco FP, Cota F, Romagnoli C. Is the prophylaxis of patent ductus arteriosus useful in extremely premature infants? Turk J Pediatr 2011; 53: 187-193.

This study was aimed to verify the efficacy and safety of ibuprofen prophylaxis of patent ductus arteriosus in very preterm infants, in order to select infants receiving higher benefits from this intervention. Two hundred neonates with gestational age (GA) ≤28 weeks receiving ibuprofen within the first two hours of life were included. Ductus closure rate was 68%, and results were significantly dependent on GA (48.8% among neonates with GA <26 weeks *vs* 73.2% among those with GA ≥26 weeks, p<0.01). Neonates with GA <26 weeks showed a lower ductus closure after the primary course of therapy (20% *vs* 57.5%, p<0.01), as well as higher reopening rate (16.2% *vs* 3.8%, p<0.05) and need for surgical ligation (38.8% *vs* 5.8%, p<0.01). During the prophylaxis period, 11 neonates (5.5%) showed pulmonary hypertension. Considering risks/benefits, we recommend prophylaxis only in infants with GA <26 weeks.

Key words: patent ductus arteriosus, COX inhibitor, ibuprofen, prophylaxis, extremely premature infants.

Patent ductus arteriosus (PDA) remains a frequent clinical problem among preterm infants and may complicate the clinical course of respiratory distress syndrome (RDS). Hemodynamically significant PDA is present in 55-70% of infants delivered prior to 28 weeks of gestational age (GA), and may require either medical or surgical treatment[1].

Cyclo-oxygenase (COX) inhibitors, as indomethacin and ibuprofen, are demonstrated to be effective in determining ductus constriction, with less negative impact of ibuprofen on organ blood flow[2-4]. Clinical and laboratory experience indicates that COX inhibitors, given as prophylaxis early after birth, are more effective in producing tight ductus constriction than waiting several days for symptoms to develop[5]. Prophylactic use of COX inhibitors has been shown to reduce the incidence of PDA, the need for rescue medical treatment and surgical closure[6]. Nevertheless, controversies still exist about an extensive use of the prophylaxis, since some preterm infants show spontaneous closure of PDA[7], and several side effects have been related to the drug use[6].

In the present study, we aimed to evaluate the short-term efficacy of prophylactic use of ibuprofen in neonates with GA ≤28 weeks to verify its usefulness and safety, in order to select infants receiving higher benefits from the prophylaxis.

Material and Methods

An observational study was performed at the Neonatal Intensive Care Unit (NICU) of the Catholic University of Sacred Heart in Rome between 1 January 2000 and 30 November 2007. Throughout this period, all inborn neonates with GA ≤28 weeks were prophylactically treated with ibuprofen. Ibuprofen was administered within two hours of life with a loading dose of 10 mg/kg followed by two maintenance doses of 5 mg/kg at 24-hour intervals. The drug was infused over 20 minutes (min) via peripheral vein or through umbilical venous catheter with tip position in

inferior vena cava. Two different formulations were used: ibuprofen lysine intramuscular formulation, Arfen® (Lysafarma, Carlo Erba, Italy) from 2000-2005 and successively intravenous (iv) ibuprofen formulation, Pedea® (Orphan, Paris, France). Exclusion criteria were: antenatal indomethacin administration, GA <23 weeks and/or birth weight (BW) <450 grams (g), congenital heart defects, persistent pulmonary hypertension, severe thrombocytopenia (platelet count $<50x10^9$/L), major congenital malformations, and premature rupture of membranes (PROM) >4 weeks.

Echocardiographic evaluation (Toshiba SSH 140A CE scanner, using a 7.5 MHz probe and a 5 MHz probe for Doppler examination) was performed immediately after birth (T0), at 72 hours of life (T72), namely 24 hours after the last prophylactic dose, and then whenever clinical suspicion of PDA occurred. Echocardiographic evaluation at T0 was aimed to verify the absence of congenital heart defects and/or pulmonary hypertension and the presence of ductus with left to right shunt, while the one performed at T72 was to verify the prophylaxis efficacy. PDA was considered hemodynamically significant in the presence of at least two of the following criteria: left atrial/aortic root ratio more than 1.5; reverse end-diastolic flow in the descending aorta; pulsatile transductal flow (Vmax) <1.8 m/sec; and ductus diameter (>1.5 mm). When ductus arteriosus was still patent and hemodynamically significant at T72, a first therapeutic course of three doses of ibuprofen (10-5-5 mg/kg/day) was administered. In case of failure, a second course of therapy with indomethacin (3 doses of 0.2 mg/kg at 12-hour (h) intervals, administered by iv infusion over 20 min) was performed.

Indications for surgical ligation were the failure to respond to rescue medical treatment or contraindications to it (serum creatinine >1.8 mg/dl or blood urea nitrogen >20 mg/dl, and severe thrombocytopenia or evidence of bleeding).

All neonates were placed in incubators with servo-controlled temperature and relative humidity of 85%; they received parenteral nutrition according to the protocol used in our NICU. Fluid intake was planned according to the following protocol: 60 ml/kg on the 1st day of life, 70 ml/kg on the 2nd day, 80 ml/kg on the 3rd day, 100 ml/kg on the 4th day, 120 ml/kg on the 5th day, and up to 150 ml/kg at the 1st week of life. Daily adjustments were made individually on the basis of body weight, urine output and serum electrolytes. Neonates requiring mechanical ventilation were assisted with high frequency oscillatory ventilation (HFOV) and in presence of RDS, surfactant treatment was administered (200 mg/kg Curosurf®, Chiesi, Italy).

For each neonate, antenatal/neonatal risk factors and complications developed during the prophylaxis or treatment period were recorded. GA was determined by the date of the last menstrual period and by an early ultrasound scanning; in case of discrepancies, early ultrasound scanning was used. In any case, GA was always confirmed by physical examination according to the New Ballard Score[8]. Neonates with BW <10th percentile for GA were defined as small-for-gestational age (SGA) on the basis of the Italian growth curves[9]. At birth and during the prophylaxis period, BW, urine output (ml/kg/h), serum creatinine, and blood urea nitrogen were monitored. Occurrence of sepsis was evaluated during the prophylaxis period. Development of necrotizing enterocolitis (NEC)[10] or spontaneous isolated intestinal perforation (SIP) was recorded, as well as intraventricular hemorrhage (IVH) occurrence[11].

Statistical Analysis

Results are presented as mean ± standard deviation (SD) for the continuous variables and as number (percentage) for the categorical variables. Unpaired Student's t-test for parametric data, Wilcoxon rank-sum test (Mann-Whitney U test) for nonparametric data and Fisher's exact test for categorical variables were used to compare neonates achieving ductus closure following prophylactic ibuprofen with those with open ductus and neonates with different GA.

A value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using the "Stata Statistical Software: Release 10" (StataCorp LP, College Station, TX).

Results

Table I. Maternal and Neonatal Characteristics

Maternal	
Preeclampsia	34 (17.0)
HELLP syndrome	4 (2.0)
Gestational hypertension	23 (11.5)
Gestational diabetes mellitus	11 (5.5)
pPROM	62 (31.0)
Chorioamnionitis	24 (12.0)
Antenatal steroids	184 (92.0)
Complete course	109 (54.5)
Cesarean section	158 (79.0)
Neonatal	
Gestational age (wks)	26.9 ± 1.3
Birth weight (g)	855 ± 242
Male	106 (53.0)
SGA	42 (21.0)
Twin	54 (27.0)
Apgar score	
at 1 min	4.9 ± 2.2
at 5 min	7.3 ± 1.2
Intubation	128 (64.0)
Surfactant therapy	139 (69.5)
Multiple doses	43 (21.5)
Age at first dose (h)	4.3 ± 3.1
Early onset sepsis	29 (14.5)
Fluid intake (ml/kg)	
Day 1	69.6 ± 12
Day 2	86.3 ± 17
Day 3	104.8 ± 19
Day 4	128.6 ± 20

Values expressed as mean ± SD or number (percent). pPROM: Premature preterm rupture of membranes. SGA: Small-for-gestational age.

During the study period, 256 neonates with GA ≤28 weeks were admitted to our NICU. Thirty-nine of them were excluded because of contraindications to prophylaxis: GA <24 weeks and/or BW <450 g (n=19), congenital heart defects (n=1), persistent pulmonary hypertension (n=6), severe thrombocytopenia (n=2), and premature (p)PROM (n=11). Among the remaining 217 infants, 10 were excluded because of incomplete data collection, and 7 died within the first hours of life before receiving the first dose of the prophylaxis. Consequently, data were analyzed on 200 neonates receiving prophylactic ibuprofen who underwent echocardiographic evaluation both at T0 and T72. Maternal and neonatal characteristics are listed in Table I.

After the prophylactic course, the rate of ductus closure was 68% (136/200). Figure 1 presents the response to the prophylaxis and the need for back-up treatment: a first course of therapy was performed in 60 neonates with hemodynamically significant PDA at T72, obtaining a closure rate of 45% (27/60); the second course of therapy was required in 22 neonates with a closure rate of 36% (8/22); finally, 23 neonates (11.5%) required surgical ligation.

Figure 2 shows the closure rate after prophylaxis, according to GA. Furthermore, Table II presents the response to the first and second course of therapeutic treatment in neonates with GA

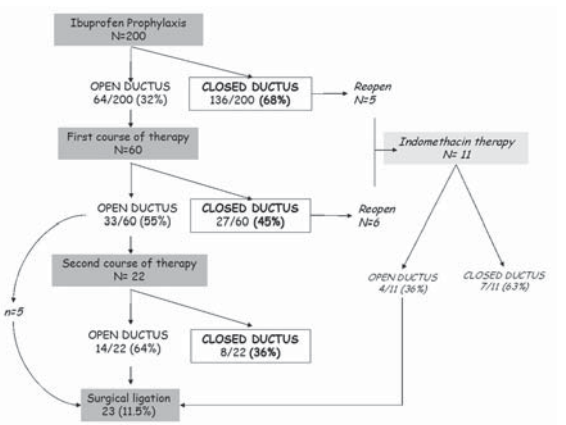

Fig. 1. Outcome of neonates treated with ibuprofen prophylaxis.

<26 weeks and in those with GA ≥26 weeks: neonates with lower GA showed a significantly lower closure rate with respect to neonates with higher GA after both the prophylaxis and the first course of therapy (p<0.01), while no difference was noticed concerning the efficacy of the second course of therapy.

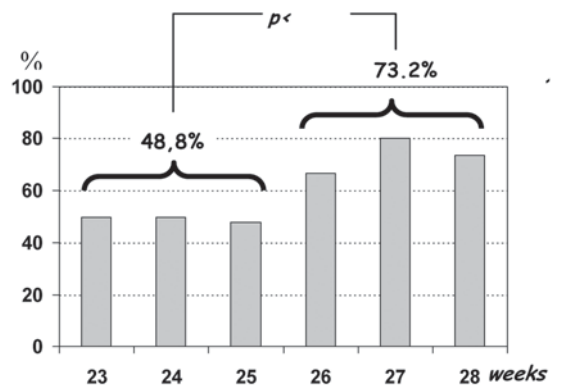

Fig. 2. Incidence of ductus closure after ibuprofen prophylaxis according to GA.

Table II. Ductus Closure According to Gestational Age and Prophylactic or Therapeutic Treatment

	<26 weeks	≥26 weeks	p
After prophylaxis	21/43 (48.8)	115/157 (73.2)	<0.01
After the first course of therapy	4/20 (20.0)	23/40 (57.5)	<0.01
After the second course of therapy	3/9 (33.0)	5/13 (38.4)	ns

Values expressed as number (percent).

Clinical and echocardiographic signs of ductus reopening were observed after the 2nd week of life in 13 neonates: 7/43 (16.2%) with GA <26 weeks and 6/157 (3.8%) with GA ≥26 weeks (p<0.05). Table III shows the reopening rate according to GA and to the time of its occurrence (after prophylaxis or rescue treatment). When ductus closure was obtained after prophylaxis, the reopening rate was similar between neonates with GA <26 and ≥26 weeks (14.2% *vs* 3.4%, p: ns). On the contrary, when ductus closure was obtained after rescue treatment, the reopening rate was significantly higher among neonates with GA <26 weeks compared to those with GA ≥26 weeks (57.0% *vs* 7.1%; p<0.05). All the reopened cases were treated with indomethacin, and four of them (36%) also required surgical ligation.

Figure 3 shows the rate of surgical ligation according to GA. The need for surgical ligation statistically significantly decreased with increasing GA (r^2=0.94; p<0.001) and results were significantly greater among neonates with GA <26 weeks compared to those with GA ≥26 weeks: 32.5% *vs* 5.8% (14/43 and 9/157, respectively; p<0.01).

The side effects were examined separately during the prophylaxis period and during the rescue treatment period in neonates with closed or open ductus after prophylaxis (Table IV).

During the prophylaxis period, no differences were found between the two groups in relation to renal function (urine output and serum creatinine), NEC and SIP, independent of GA (data not shown). Eleven neonates (5.1%), 5 with closed ductus and 6 with open ductus, showed severe hypoxemia as a consequence of pulmonary hypertension, independent of GA. Pulmonary hypertension appeared immediately after the loading dose in 9 cases and after the 1st maintenance dose in 2 cases. All these neonates prompted the discontinuation of the treatment, and 6 of them received inhaled nitric oxide in addition to mechanical ventilation. A greater incidence of IVH ≥3rd grade was observed in infants with PDA as compared to infants with closed ductus at T72 (p<0.05).

During the 1st and the 2nd course of rescue therapy, a greater number of pulmonary hemorrhage (p<0.01), severe IVH (p<0.05) and SIP (p <0.05) were observed in neonates with persistently open ductus with respect to those with closed ductus at T72, without any difference in the incidence of severe thrombocytopenia and abnormal coagulation tests (data not shown).

Discussion

Ibuprofen has been proven effective for both prevention and treatment of PDA in preterm infants[6,12]. In particular, prophylactic use in high-risk preterm neonates is reported to be effective in reducing the incidence of PDA and the need for both rescue treatment with COX inhibitors and surgical ligation, although it may unnecessarily expose a proportion of infants to this drug and therefore to its

Table III. Number of Reopened Ductus According to GA

	<26 weeks (n = 43)	≥26 weeks (n = 157)	p
Reopening ductus	7 (16.2)	6 (3.8)	<0.05
After prophylactic closure	3/21 (14.2)	4/115 (3.4)	
After rescue therapy closure	4/7 (57.0)	2/28 (7.1)	<0.05
Surgical ligation after reopening	3/7 (42.9)	1/6 (16.6)	<0.05

Values expressed as number (percent).

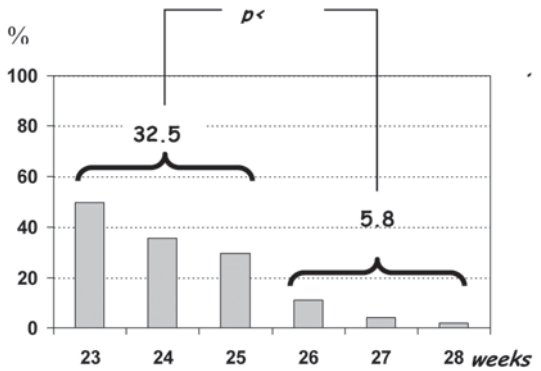

Fig. 3. Surgical ligation related to GA.

side effects[6]. In fact, some preterm infants, despite their extreme immaturity, show a spontaneous closure of the ductus. According to the literature, the rate of spontaneous closure shows a great variability[13,15] and in infants with 23-27 weeks of GA, it is found in 24%[16].

Our study, although it did not include a control group, was carried out in a single institution and included a larger number of neonates with GA ≤28 weeks if compared to the studies analyzed in the recent Cochrane review regarding the prophylactic use of ibuprofen[6].

We found that prophylactic ibuprofen induced a closure rate of 68%, similar to the data reported by Gournay et al.[15] in a multicenter, randomized, double blind trial regarding neonates <28 weeks of GA. In our study, GA was the main factor influencing the prophylaxis efficacy, response to medical treatment, and reopening of the ductus, as well as the need for surgical ligation.

Regarding the prophylaxis response, Chorne et al.[17] recently emphasized that GA directly affects the likelihood of ductal closure with indomethacin use. In our experience, carried out with ibuprofen, the lower closure rate showed among neonates with GA <26 weeks compared to those with GA ≥26 weeks may reflect the peculiar intrinsic characteristics of more preterm ductus.

Indeed, preterm ductus, due to its anatomic intrinsic characteristics[17,18], requires a tighter degree of constriction to reach definitive closure. As a consequence, as GA advances, spontaneous ductus closure progressively increases[7].

In our study, GA also played an important role in the response to the first rescue medical treatment after failure of prophylaxis, resulting in a higher closure rate at higher GA. The response to medical treatment was recently analyzed by Madan et al.[19] among neonates with GA ≤30 weeks who received indomethacin treatment for symptomatic PDA. In that study, the likelihood of ductus closure increased linearly with advancing GA through 27 completed weeks' gestation, after which it did not increase.

According to our experience, postnatal age also influenced the effectiveness of rescue therapies, since we observed a ductus closure rate of 45%

Table IV. Clinical Complications According to Ductus Closure at T72, During and After Prophylaxis

	Closed ductus (n = 136)	Open ductus (n = 64)	p
During prophylaxis period			
Urine output <1 ml/kg/h	18 (13.2)	10 (15.6)	
Serum creatinine >1.8 mg/dl	12 (8.9)	7 (12.0)	
Necrotizing enterocolitis	1 (0.7)	1 (1.6)	
SIP	1 (0.7)	-	
Pulmonary hypertension	5 (3.7)	6 (9.4)	
IVH ≥ 3rd grade	3 (2.2)	8 (12.5)	<0.05
During rescue therapy period			
Pulmonary hemorrhage	7 (5.1)	11 (17.2)	<0.01
Necrotizing enterocolitis	9 (6.6)	6 (9.3)	
SIP	2 (1.4)	6 (9.4)	<0.05
IVH ≥ 3rd grade	4 (2.9)	7 (10.9)	<0.05

Values expressed as number (percent).
SIP: Spontaneous isolated intestinal perforation. IVH: Intraventricular hemorrhage.

after the first course of therapy and 36% after the second. These results confirm that the effectiveness of COX inhibitors progressively wanes with increasing postnatal age[20], maybe because of an increased nitric oxide production in the ductus wall[21].

Furthermore, in our study, the risk of ductus reopening were greater at lower GA, confirming that in extremely preterm neonates, the ductus frequently fails to develop the level of profound hypoxia-ischemia needed to cause anatomic remodelling and smooth muscle death, although a functional constriction is obtained[22].

A direct consequence of a lower effectiveness of both prophylaxis and therapy among neonates with lower GA is the higher need for surgical ligation.

Concerning side effects of ibuprofen prophylaxis, pulmonary hypertension occurred in 11 neonates (5.5%) in our series. Gournay et al. [23] have already alerted neonatologists about the occurrence of pulmonary hypertension after the loading dose of ibuprofen, hypothesizing that very early administration of ibuprofen (within the first 6 hours of life) might prevent the normal decrease in pulmonary vascular resistance and interfere with the physiologic peak of prostaglandin activity, markedly high in the early postnatal period in very preterm infants[24]. Indeed, among the 11 neonates with pulmonary hypertension, we observed that four neonates also had twin-to-twin transfusion syndrome, and five were born to mothers with severe oligohydramnios. We cannot exclude that, in addition to ibuprofen administration, other factors could play a role in determining this severe complication.

As for side effects observed after the prophylaxis period, it is possible that persistent ductus patency rather than rescue treatment with COX inhibitors (ibuprofen and indomethacin) could represent the main risk factor not only for IVH and pulmonary hemorrhage but also for SIP occurrence[25]. In fact, the significantly higher number of neonates with SIP in the open ductus group and its late onset led us to presume that this complication is not related to prophylactic ibuprofen administration but rather to other factors. It is known that ibuprofen, compared with indomethacin, does not significantly reduce mesenteric blood flow[3] and it does not induce any macroscopically visible damage of the intestinal mucosa[26].

In conclusion, although the management of PDA in premature neonates has always been a challenge to the neonatologists and continues to be a controversial topic, we believe that prophylactic more than therapeutic strategy is suitable for neonates with GA <26 weeks. In very immature infants, in fact, the likelihood of spontaneous ductus closure is low[16], and a more successful closure rate is obtained when the treatment is administered early. Furthermore, as recently highlighted by Richards et al.[27], in infants of <26 weeks' GA, the therapeutic strategy is related with a higher rate of surgical ligation, even when multiple courses of treatment are administered.

Furthermore, in this high-risk population, early ductus closure has the benefit of reducing the need for multiple courses of COX inhibitors, the effectiveness of which progressively decreases with increasing postnatal age and the side effects of which should not be underestimated.

Nevertheless, in order to reduce the incidence of severe side effects of the prophylaxis, such as pulmonary hypertension, a careful evaluation of all factors able to interfere with the physiologic decrease in pulmonary resistances is necessary before prophylaxis. Moreover, a later administration of the drug after birth is preferable and a longer duration of ibuprofen loading dose infusion may also be considered.

Regarding neonates with GA ≥26 weeks, considering the high likelihood of either spontaneous or pharmacologic ductus closure and the low need for surgical ligation, we believe that an early-targeted treatment, led by longitudinal observations of the changes in Doppler pattern[28], could reduce possible overtreatment and COX-inhibitor-induced adverse effects.

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