Kepada Yth:
dr. Theodorus M.Med

Abstract TEVIV

ISSN 0030-9311

53 • No. 3 • May 2013

Paediatrica Indonesiana

(The Indonesian Journal of Pediatrics and Perinatal Medicine)

In this issue

Published by
Indonesian Pediatric Society

Paediatrica Indonesiana

VOLUME 53 May • 2013 NUMBER 3

Original Article

Ibuprofen vs. indomethacin for persistent ductus arteriosus closure in preterm infants

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Abstract

Background Indomethacin and ibuprofen are anti-prostaglandin E2 agents administered for persistent ductus arteriosus (PDA) closure. Ibuprofen has weaker cyclooxygenase-1 inhibitor affinity than that of indomethacin, causes decreased gastrointestinal circulation, as well as brain and kidney side effects.

Objective To compare the efficacy of oral ibuprofen and indomethacin for PDA closure in preterm infants.

Methods A randomized double-blind controlled trial on preterm infants with PDA was performed in Mochammad Hoesin Hospital, Palembang, from October to December 2011. Persistent ductus arteriosus was diagnosed by echocardiography. Subjects were divided into two groups, and received either ibuprofen or indomethacin. Ibuprofen was given at a dose of 10 mg/kgBW/d on day 1 and 5 mg/kgBW/d on days 2 and 3. Indomethacin was given in three doses over 24 hour-intervals; the first dose was 0.2 mg/kg, and the second and third doses were 0.1 mg/kg each.

Results Sixty infants were enrolled in this study, 36 boys (60%) and 24 girls (40%). Fifty-two subjects completed the study protocol. Ductus arteriosus (DA) closure after treatment was observed in 22 out of 26 subjects in the ibuprofen group and 19 out of 26 subjects in the indomethacin group (P=0.04). The mean DA diameter reductions after administration of ibuprofen or indomethacin were 0.40 (SD 0.16) mm and 0.30 (SD 0.24) mm, respectively (95%CI of differences 0.05 to 0.17; P=0.04). Serum creatinine was elevated in the indomethacin group following treatment compared to the ibuprofen group [P = 0.002, 95% CI of differences 0.06 to 0.27]. Ductus arteriosus reopening occurred in 4 out of 19 subjects in the indomethacin group, while none in the ibuprofen group.

Conclusions Ibuprofen is better than indomethacin, in terms of higher PDA closure rate and mean DA diameter reduction after treatment. In additional, indomethacin has significantly greater increase in mean serum creatinine level after treatment than ibuprofen. **[Paediatr Indones. 2013;53:138-43.]**

Keywords: persistent ductus arteriosus, preterm infants, ibuprofen, indomethacin.

Ductus arteriosus (DA) closure in preterm infants is mandatory before complications occur that prohibit the administration of pharmacologic agents. Indomethacin is an effective drug for DA closure in preterm infants. It has two isoforms: cyclooxygenase-1 (COX-1) inhibitor and cyclooxygenase-2 (COX-2) inhibitor, of which the COX-1 inhibitor is stronger.[1-4] Ibuprofen is another anti-prostaglandin agent of similar efficacy, but fewer side effects compared to indomethacin. Indomethacin is more costly and less widely available than ibuprofen. Until now, there have been few reports on the comparative efficacy of these two agents in the Moehammad Hoesin Hospital, Palembang. The current standard of treatment for persistent ductus arteriosus (PDA) in Moehammad Hoesin Hospital is indomethacin.

The aims of this study were to compare the efficacy of ibuprofen and indomethacin in preterm infants with PDA, and to assess the time needed for DA closure for each intervention.

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Paediatrica Indonesiana

Indonesian Journal of Pediatrics and Perinatal Medicine

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Subscription rate:
Indonesia: Rp 180.000,- per year
All other countries: US $ 100 per year
Single copy: Rp 30.000,- or US $ 20
Shipping cost for outside Jabodetabek is not included
(Valid until December 2013)

Methods

A randomized double-blind controlled trial was conducted in the Department of Neonatology, the Neonatal Intensive Care Unit, and the Rooming-in Nursery in the Department of Child Health at Mohammad Hoesin Hospital, Palembang from October to December 2011.

All preterm infants of less than 37-week gestation with PDA confirmed by echocardiography were studied. We excluded infants with renal dysfunction (diuresis <1 cc/kg/h and creatinine serum level ≥ 1.3 mg/dL), platelet count < 50,000/mm^3, ductal-dependent congenital heart disease, major congenital anomalies, necrotizing enterocolitis, intraventricular haemorrhage (grades III-IV), or neonatal septicemia. Persistent ductus arteriosus was confirmed by echocardiography using a *Philips® HD7 XE* with s-8 transducer.

Subjects were numbered 1 to 60 then divided into two groups by consecutive sampling, either the ibuprofen or indomethacin group. Ibuprofen was given at a dose of 10 mg/kgBW/d on day 1 and 5 mg/kgBW/d on days 2 and 3. Indomethacin was given in three doses in 24-hour intervals. The first dose was 0.2 mg/kgBW, and the second and third doses were 0.1 mg/kgBW.

The parameters of treatment response were DA closure and diameter reduction, taken in serial measurements. Ductus arteriosus reopening was defined as a DA that reopened after closure, as determined by echocardiographic evaluation after three doses of oral ibuprofen or indomethacin administration.

Ductus arteriosus monitoring was performed using echocardiographic examinations (days 1, 2, 3, 4, and 7), or transfontanellar ultrasound (days 1 and 4). Monitoring of side effects was performed by routine blood tests, C-reactive protein (CRP) level, and renal function tests on days 1 and 4. During treatment, diuresis was monitored daily.

Subjects were considered to have dropped out of the study if the following occurred: death before 7 days of medication or before echocardiographic examination for the full 7 days to monitor reopening, septicemia, bleeding, gastrointestinal perforation, necrotizing enterocolitis, or decreased renal function in the first to third days of medication administration.

The Ethics Committee of Sriwijaya University Medical School, Palembang, Indonesia approved this study. Informed consent was obtained from all parents.

Statistical significance was set at the 95%CI level. Differences between groups were analyzed by student's T-test. Differences in proportions between the two groups were analyzed with Fisher's exact and Chi-square tests. Survival rate was analyzed with Kaplan-Meier test.

Results

Of the 82 preterm infants admitted to Mohammad Hoesin Hospital, Palembang, 60 subjects with PDA were enrolled in this study. Subjects were divided into two groups of 30 each, the ibuprofen group and the indomethacin group. The basic characteristics of subjects are shown in **Table 1**.

Four infants in the ibuprofen group and four in the indomethacin group dropped out due to pulmonary hemorrhage (5 infants), discharge to another hospital (1 infant), or gastrointestinal bleeding before completing three doses medication (2 infants).

In paired T-test revealed a significant difference in DA diameter reduction by 0.36 (SD 0.16) mm with P=0.00 (95%CI 0.29 to 0.43) in the ibuprofen group, and 0.32 (SD 0.21) mm with P=0.00 (95% CI 0.22 to 0.40) in the indomethacin group (**Table 2a, Table 2b**).

Patients with PDA closure after three doses of oral ibuprofen were 22 out of 26 subjects and oral indomethacin were 19 out of 26 subjects; it was a significant difference (P= 0.04).

Unpaired T-test was also performed to compare DA constriction after three doses of oral ibuprofen and indomethacin. Similarly, there was a significant difference between the two groups (P=0.04; 95%CI 0.05 to 0.17). By Kaplan-Meier survival analysis, we found no significant difference in mean days to closure in the ibuprofen and indomethacin groups, with 2.8 (SD 0.2) days and 3.2 (SD 0.2) days, respectively, (P= 0.16). Side effects after three doses of medication are shown in **Table 3a** and **Table 3b**.

One infant in the indomethacin group had increased plasma creatinine to 1.6 mg/dL and decreased diuresis to 0.8 cc/kg/h. Serum creatinine

was monitored before and after therapy for both groups. We found no significant difference in the mean serum creatinine level (0.02 mg/dL) before and after ibuprofen administration [P=0.60, (SD 0.03); 95%CI 0.05 to 0.09]. However, mean serum creatinine level (0.17 mg/dL) before and after indomethacin administration was significantly different [P=0.09, (SD 0.03); 95%CI 0.08 to 0.23].

There was significantly higher creatinine serum elevation after indomethacin administration com-

Table 1. Characteristics of subjects

Characteristics	Ibuprofen group (n= 30)	Indomethacin group (n= 30)
Sex, n		
Male	16	20
Female	14	10
Mean age (SD), hours	29.7 (9.2)	28.9 (7.9)
Mean gestational age (SD), weeks	33 (2.4)	31.7 (3.4)
Mean birth weight (SD), grams	1,793.3 (395.4)	1,711.7 (498.9)
Respiratory dysfunction, n		
None	9	6
Bronchopneumonia	8	10
Hyaline membrane disease	5	9
Transient tachypnea of the newborn	8	5
Echocardiography results, n		
Flow type		
Growing	22	26
Pulsatile	8	4
PDA size		
Small	3	4
Moderate	25	25
Large	2	1
CHD		
None	17	22
TR	9	7
PFO	2	0
ASD	0	1
AVSD	1	0
VSD	1	0

CHD= congenital heart disease; TR= tricuspid regurgitation; PFO= patent foramen ovale; ASD= atrial septal defect; AVSD= atrioventricular septal defect; VSD= ventricular septal defect

Table 2a. Mean ductus arteriosus diameter before and after treatment with ibuprofen or indomethacin

Treatment groups	Mean ductus arteriosus diameter (SD), mm		95%CI of diameter reduction	P value
	Before	After		
Ibuprofen (n= 26)	0.43 (0.11)	0.07 (0.16)	0.29 to 0.43	0.00
Indomethacin (n= 26)	0.44 (0.13)	0.12 (0.21)	0.22 to 0.40	0.00

Table 2b. Response to treatment with ibuprofen or indomethacin.

Variables	Ibuprofen group (n= 26)	Indomethacin group (n= 26)	P value
DA closure, n	22	19	0.04
DA did not close, n	4	7	0.04
Mean DA diameter reduction after treatment (SD), mm	0.36 (0.16)	0.32 (0.21)	0.04
Mean time until DA closure (SD), days	2.8 (0.2)	3.2 (0.2)	0.16
DA reopened, n	0	4	0.00

Table 3a. Side effects of medications by treatment group

Variables	Treatment		P value
	Ibuprofen group (n= 26)	Indomethacin group (n= 26)	
Side effects			
Thrombocytopenia	4	5	
Skin hemorrhage	2	1	
Gastrointestinal bleeding	0	2	
Peri Intra Ventricular Hemorrhage	1	3	
Renal function disorder	0	1	
None	19	14	
Mean plasma creatinine difference before and after treatment (SD), mg/dL	0.02 (0.1)	0.17 (0.19)	0.002

Table 3b. Mean plasma creatinine level before and after treatment with ibuprofen or indomethacin

Treatment groups	Mean plasma creatinine level (SD), mg/dL		95% CI differences between before-after	P value
	Before	After		
Ibuprofen (n= 26)	0.77 (0.25)	0.75 (0.28)	0.05 to 0.09	0.60
Indomethacin (n= 26)	0.72 (0.25)	0.89 (0.28)	0.08 to 0.23	0.09

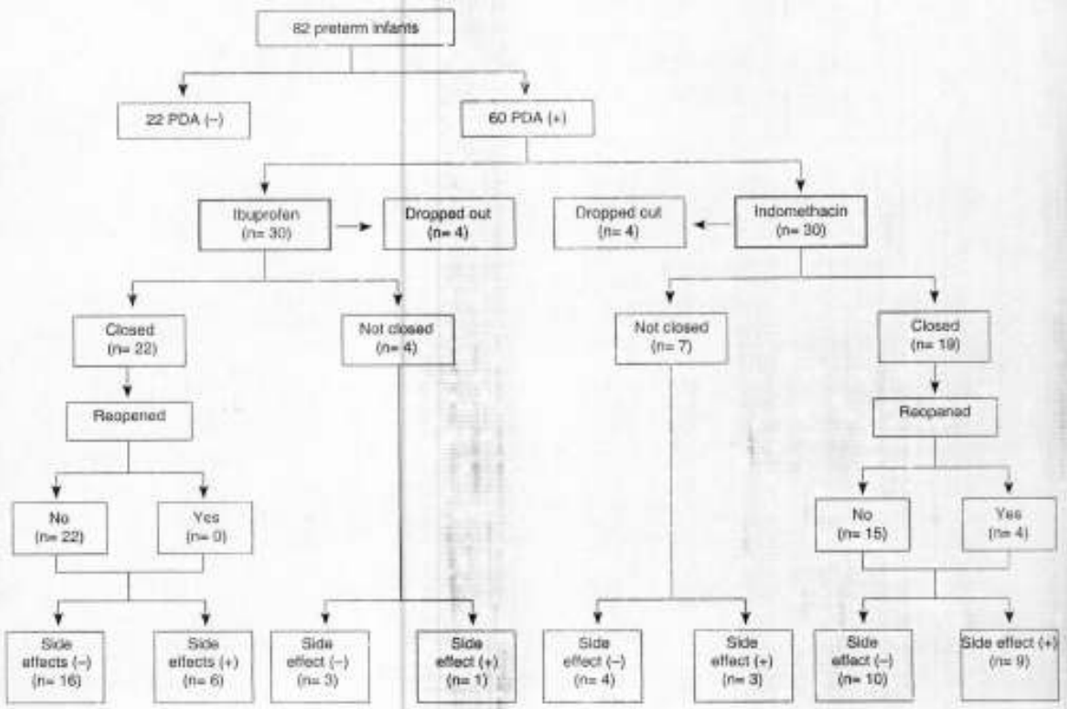

Figure 1. Consort diagram of infants with PDA treated with either oral ibuprofen or oral indomethacin

pared to that of three doses of ibuprofen [mean 0.17 mg/dL, P=0.002, (SD 0.05); 95%CI 0.06 to 0.27].

As shown in **Figure 1**, the consort diagram of preterm infants with PDA, we noted that 4 infants failed to respond to treatment in the ibuprofen group and 7 infants failed in the indomethacin group. Ductus arteriosus reopening occurred in 4 infants in the indomethacin group, but none occurred in the ibuprofen group.

Discussion

From 82 preterm infants, 60 infants (73%) with PDA met our inclusion criteria. Similarly, Sekar *et al.* showed that the incidence rate of PDA in preterm infants was 70%.[3]

In our study, there were 36 boys (60%) and 24 girls (40%). Ages varied from 16 to 48 hours. The first echocardiography was performed when the subject's age was at least 15 hours. According to reports by Park and Coceani *et al.*, DA closure functionally occurs within 10-15 hours after birth.[2,5]

After three doses of ibuprofen or indomethacin administration, DA closure occurred in 22 out of 26 subjects in the ibuprofen group and 19 out of 26 in the indomethacin group, respectively. Heyman *et al.* reported that the effectiveness of ibuprofen was 95.5%.[6] Also, Fanos *et al.* and Richard *et al.* reported the efficacy of ibuprofen to be 80% and 83%, respectively.[7,8] Furthermore, DA diameter reduction was significantly greater in the ibuprofen group (P=0.04; 95% CI 0.05 to 0.17). From Kaplan-Meier survival test analysis, the mean time until DA closure was 2.8 days. Similarly, Overmeire *et al.* reported that the mean closure day was at the third and fourth days.[9]

Thrombocytopenia was found in five of 26 infants given oral indomethacin. Ibuprofen is a weaker COX-1 isoform compared to indomethacin. Allegaert *et al.* reported that there are fewer renal side effects from ibuprofen than indomethacin.[10] We found decreased renal function in 1 infant who was given indomethacin, with a creatinine level of >1.3 mg/dL after treatment and urine volume of 0.8 cc/kg/h. This finding was similar to that of Van Overmeire *et al.*, who showed that serum creatinine elevation occurred 1-4 days after indomethacin administration.[9] Serum creatinine was significantly more elevated after three doses of indomethacin compared to three doses of ibuprofen.[10]

Ductus arteriosus reopening occurred in 4 of 19 (21%) previously closed DA patients in the indomethacin group, while none reopened in the ibuprofen group. Similarly, Heyman *et al.* reported no DA reopening in the ibuprofen group.[6] Quinn *et al.* reported that the incidence rate of DA reopening after oral indomethacin administration was 17%.[11]

Reopening may be caused by pulmonary disorders. The mechanism involved response of DA to prostaglandin-E2 (PGE2), and low oxygen pressure.[11] In condition of pulmonary disorders, elimination of PGE2 in the lung will decrease, therefore the level of PGE2 will rise. In pulmonary disorders, the oxygen pressure also decreases to hypoxia and acidosis that will lead to the relaxation of DA. Pulmonary disorders found in our subjects were pneumonia, hyaline membrane disease, and transient tachypnea of the newborn.

A limitation of this study was the occurrence of complications, such as septicemia, hyaline membrane disease, and other pulmonary diseases. It was also difficult to monitor patients for long periods due to the high incidence of morbidity and mortality. In additional, the side effects that may arise due to the intervention or complication, often occurs in premature infants.

In conclusion, there is a significant difference in the closure of DA after ibuprofen administration compared to that of indomethacin. Also, DA diameter reduction is significantly greater after ibuprofen administration compares to that of indomethacin. There is also a significantly higher serum creatinine elevation after indomethacin administration compares to that of ibuprofen.

Acknowledgment

We would like to thank the pediatricians, H. Bernawi and A. Ramadanti, and the pharmacists, Amrizal, E. Yunita, C. Wilia, and Henny, for their contributions to this study.

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