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Original Article

Intravenous paracetamol and patent ductus arteriosus closure in preterm infants

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Abstract

Background Indomethacin and ibuprofen are the drugs of choice for closure of patent ductus arteriosus (PDA) in preterm infants. However, intravenous preparations are of limited availability in Indonesia. Circumstantial evidence has shown that intravenous paracetamol may be an alternative therapy for PDA closure in premature infants.

Objective To evaluate the effect of intravenous paracetamol on PDA closure in preterm infants.

Methods A before-and-after study was conducted between May and August 2014 in Cipto Mangunkusumo General Hospital, Jakarta in preterm infants with hemodynamically significant PDAs, as established by echocardiography using the following criteria: duct diameter >1.4 mm/kg, left atrium to aorta ratio >1.4, and mean velocity in the left pulmonary artery >0.42 m/s or mean diastolic velocity in the left pulmonary artery >0.2 m/s. Subjects, aged 2 and 7 days, received intravenous paracetamol (15 mg/kg every six hours) for 3 days. Paired T-test was used to compare pre-intervention PDA diameter to those assessed at 24 hours after the intervention and at 14 days of life.

Results Twenty-nine subjects had a mean gestational age of 30.8 weeks and mean birth weight of 1,347 grams. Nineteen (65.5%) patients had closed PDAs at the day 14 evaluation, 1 experienced PDA reopening, and 9 had failed PDA closure. No liver toxicity was identified. Mean duct diameters before, 24 hours after the intervention, and at 14 days of life were 3.0, 0.9, and 0.6 mm, respectively (P<0.0001).

Conclusion Intravenous paracetamol seems to be reasonably effective for PDA closure in preterm infants. **[Paediatr Indones. 2017;57:198-203 ; doi: http://dx.doi.org/10.14238/pi57.4.2017.198-203]**.

Keywords: *intravenous paracetamol; patent ductus arteriosus; preterm neonates*

Patent ductus arteriosus (PDA) is a common clinical problem encountered in preterm neonates. The three management approaches for PDA in preterm infants are conservative monitoring, medical treatment, or surgical ligation, depending on the hemodynamic significance of the shunt and associated comorbidities.[1] With regards to medical treatment, indomethacin and ibuprofen are anti-prostaglandin drugs widely used for PDA closure in preterm infants. However, these drugs are may have severe adverse events, such as acute kidney injury associated with indomethacin use, or gastrointestinal bleeding with ibuprofen.[2] Another issue is the limited availability of intravenous preparations, which are often required for sick infants who are contraindicated for oral or enteral intake. Therefore, in this setting, preterm infants with significant PDAs often have to proceed directly to surgical ligation, which carries higher risks of morbidity and mortality.[3]

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Paracetamol, a widely available non-steroidal anti-inflammatory drug, also has an anti-prostaglandin effect, but through a different mechanism from indomethacin, ibuprofen, or other non-selective cyclooxygenase (COX) inhibitors. Paracetamol acts as a peroxidase inhibitor in prostaglandin synthesis.4 In previous case series involving a limited number of subjects, both oral[5-12] and intravenous preparation[12-15] of paracetamol showed satisfactory results for PDA closure, with no liver toxicity. Moreover, two randomized, double-blind, control trials showed that oral paracetamol was better than oral ibuprofen.[16,17] However, as evidence for intravenous paracetamol was from anecdotal case reports, so far it has not been recommended as a drug of choice for PDA closure in neonates, although it may serve as an alternative drug, particularly for preterm infants with contraindications for oral or enteral intake.

This study aimed to evaluate the effect of intravenous paracetamol on PDA closure in preterm infants.

Methods

A before-and-after study was conducted between May and August 2014 in the neonatal intensive care unit (NICU), Cipto Mangunkusumo General Hospital, Jakarta. We enrolled infants aged 2 to 7 days, with gestational age less than 36 weeks and birth weight less than 2,000 grams, who had PDAs and were contraindicated for enteral intake. A PDA was defined as hemodynamically significant (hs-PDA) if the duct diameter was more than 1.4 mm/kg, left atrium to aorta (LA/Ao) ratio was more than 1.4, mean velocity in the left pulmonary artery was more than 0.42 m/s or mean diastolic velocity in the left pulmonary artery was more than 0.2 m/s. Based on a previous study, the sensitivity and specificity of these criteria were above 90%.20 The 2D and Doppler echocardiography were performed using a *Philips® HD11XE* ultrasound machine with a 12 MHz transducer. Duct diameter was measured by parasternal short axis view. We excluded infants with major congenital anomalies, other congenital heart diseases (except persistent foramen ovale), persistent pulmonary hypertension of the newborn (PPHN), hyperbilirubinemia requiring exchange transfusion, neonatal hepatitis before intervention, and infants who died before completing the intervention. This study was approved by the Research Ethics Committee, University of Indonesia Medical School, Jakarta. Written informed consent was obtained from parents before intervention.

All subjects underwent baseline clinical examinations such as assessment of gestational age based on the New Ballard Score (NBS), birth weight, biological sex, Apgar scores, vital signs, and routine blood tests. We administered bolus intravenous paracetamol (15 mg/kg) every 6 hours for 3 days. Echocardiographic evaluations to assess PDA diameter were performed 24 hours after the first intervention, 24 hours after the second intervention, and at 14 days of life. The second 3-day intervention with the same drug and dose was given if the child's PDA persisted after the first intervention. A complete closure was defined as a closed PDA at 14 days of life. Otherwise, the treatment was considered to have failed. We also recorded any adverse events, including mortality. We stopped the intervention if patients developed a significant elevation in serum transaminase levels. The study would be terminated if there was a subject died due to neonatal hepatitis.

Clinical characteristics and echocardiographic findings were described as a proportion or mean (standard deviation, SD), as appropriate. Paired T-test was used to compare PDA diameters before intervention to those 24 hours after the first or second intervention, and on day 14. A P value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed using *SPSS for Windows version 18.0*.

Results

A total of 171 preterm infants were treated in our hospital, but only 127 (74.3%) infants underwent echocardiography examinations due to other clinical conditions of hemodynamic significance, such as respiratory disorders, history of asphyxia, tachycardia, heart enlargement based on chest X-ray, gastrointestinal bleeding, or other conditions suggesting contraindications of oral therapy. Echocardiography was also not conducted on babies in critical condition in the emergency room. In addition, three infants with congenital anomalies, two infants with complex congenital heart

diseases (transposition of the great arteries and complete atrioventricular septal defect), and two infants with PPHN were excluded.

Thirty-six infants (28.3%) were found to have patent ductus arteriosus/PDA. Twenty-nine (80.6%) subjects completed the entire study protocol (**Figure 1**). The clinical characteristics and echocardiographic findings are summarized in **Table 1**. After the first intervention, 21 (61.8%) subjects were defined to have PDA closure. After the second intervention, of 13 subjects with closure failure after the first intervention, 4 (11.8%) subjects had PDA closure. At 14 days of life, 19 (55.9%) subjects had been successfully treated, and 10 (34.5%) subjects had treatment failure, including one subject with reopening of the PDA.

The mean PDA diameters significantly decreased between before intervention and after the first intervention, after the second intervention, and at 14 days of life. However, the mean PDA diameter did not significantly decrease between after the second intervention and at 14 days of life (**Table 2**). Seven infants died because of severe sepsis and multiple organ system failure. Three cases experienced intraventricular hemorrhage (IVH) grade III/IV and one case had gastrointestinal bleeding. No necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), or retinopathy of prematurity (ROP) were observed. Subjects' median aspartate transaminase (AST) level was 16 (4-42) U/L and median alanine transaminase (ALT) level was 8 (4-20) U/L.

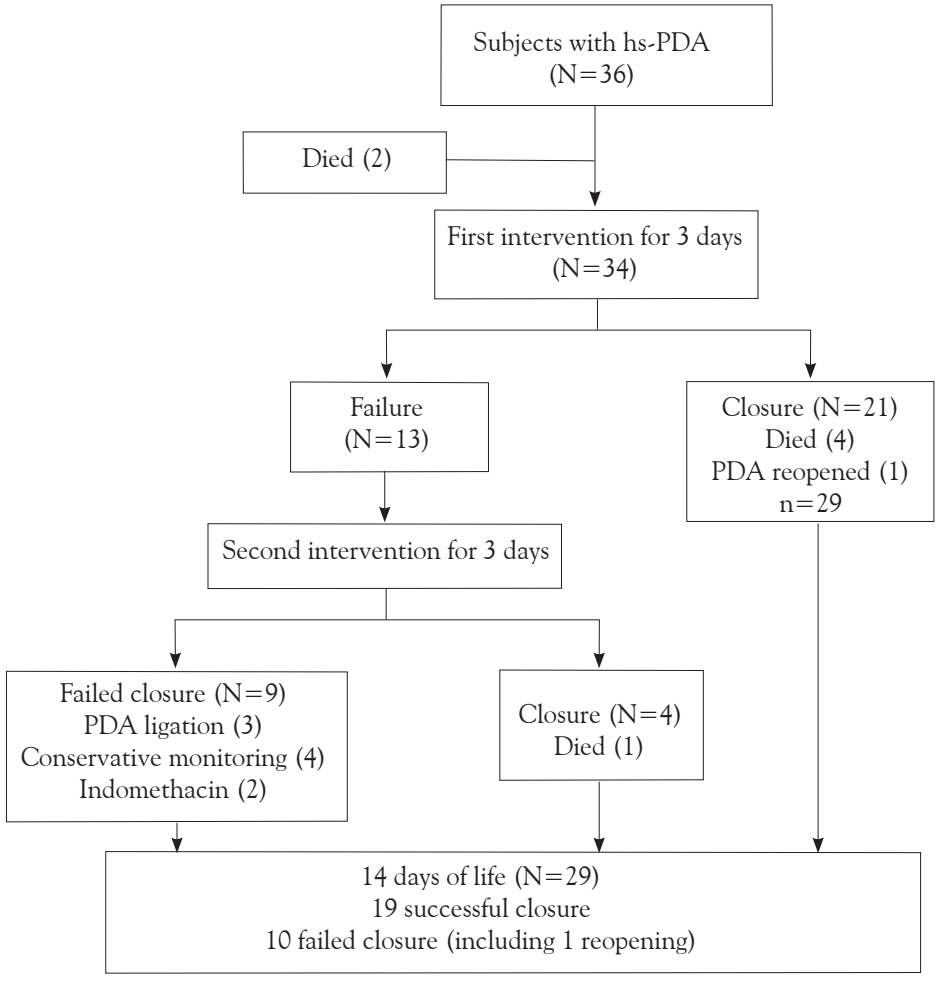

Figure 1. Flow diagram of study

Table 1. Clinical characteristics and echocardiographic findings

Characteristics	N=36
Gender	
Male, n	18
Female, n	18
Gestational age	
Mean (SD), weeks	30.8 (2.52)
< 32 weeks, n	25
33-36 weeks, n	11
Birth weight	
Mean (SD), grams	1347 (285.3)
< 1,500 grams, n	23
1,500-2,000 grams, n	13
Median (range) chronological ag at enrollment, hours	72 (49-165)
Median Apgar score (range)	
At 1 min	6 (1-9)
At 5 min	8 (3-10)
Platelet < 60,000/mL, n	2
Platelet 60,000-150,000/mL, n	10
Neonatal asphyxia, n	10
Respiratory distress syndrome grade III/IV, n	12
Apneua of premturity, n	19
Heart rate > 180 bpm, n	15
Murmur, n	9
Heart enlargement, n	6
Hyperbilirubinemia requiring phototherapy, n	12
Supportive therapy	
Nasal CPAP, n	20
Mechanical ventilation, n	16
Antibiotic	
Ampicillin-sulbactam + gentamicin, n	8
Pipercillin-tazobactam + amikacin, n	25
Metropenem, n	3
Total parenteral nutrition,	3
Blood transfusion, n	6
Echocardiographic findings	
Mean duct diameter (SD), mm	3.0 (0.54)
Mean LA/Ao ratio (SD)	1.8 (0.32)
Mean flow velocity in left pulmonary artery (SD), m/s	0.8 (0.25)
Mean diastolic flow velocity in left pulmonary artery (SD), m/s	0.4 (0.19)

Table 2. The differences of PDA diametera at before, after first, and after second intervention, and at 14 days of life

Characteristics	n	Mean diameter (SD), mm	Difference (SD)	P value
Before intervention	34	3.0 (0.55)	2.1 (1.04)	<0.0001
After first intervention		0.9 (1.18)		
Before intervention	34	3.0 (0.55)	2.4 (1.00)	<0.0001
After second intervention		0.6 (0.61)		
Those who failed after first intervention	13	2.2 (0.70)	0.8 (1.04)	0.016
After second intervention		1.4 (1.11)		
Before intervention	29	3.0 (0.57)	2.4 (0.91)	<0.0001
Chronological age 14 days		0.6 (0.98)		
After first intervention	17	0.9 (1.19)	0.3 (0.87)	0.059
Chronological age 14 days		0.6 (0.98)		
After second intervention	12	0.6 (1.03)	0.0 (0.52)	0.630
Chronological age 14 days		0.6 (0.98)		

Notes: 34=total number of infants enrolled in the first intervention, 13=total number of infants in failure group & enrolled in the second intervention, 17=total number of infants in closure group, 12=total number of infants enrolled in the second intervention.

Discussion

The incidence of PDA in preterm infants is estimated to be 20 to 60%. Incidence rates are higher in small for gestational age and extremely low birth weight (ELBW) infants. In infants with birth weight below 1,200 grams, the incidence of PDA is approximately 80%. However, in those with birth weight below 2,500 grams, it is approximately 30%.18 In this study, we used birth weight criteria below 2,000 grams and gestational age below 36 weeks. Beyond gestational age and birth weight, the incidence of hemodynamically significant PDA was also dependent on diagnostic criteria based on clinical manifestations and echocardiography. Approximately 34% of PDA cases in preterm infants may close spontaneously at the chronological age of about 2 to 7 days, depending on the presence of hemodynamic disorders.[19]

Before the intervention, 10 subjects had neonatal asphyxia, 12 had respiratory distress syndrome (RDS), [19] had apnea of prematurity (AOP), 12 had thrombocytopenia, 12 had hyperbilirubinemia requiring phototherapy, and all subjects were suspected to have sepsis. We did not analyze the effect of these conditions on the success of the treatment, i.e., PDA closure. These conditions are considered complex problems for the management of preterm infants in tertiary hospitals in Indonesia. Nevertheless, subjects continued to receive supportive treatment based on clinical practice guidelines in our hospital.

We included 36 (28.3%) preterm infants with hs-PDA. Echocardiography examination was performed after the chronological age of about 72 hours. Although it is possible for PDA to close spontaneously in infants within the age range, we used the clinical hemodynamic consideration criteria for giving intravenous paracetamol. The incidence of PDA was difficult to precisely determine because not all preterm infants in our hospital undergo echocardiographic examination. Some infants died in the emergency room before this examination was done.

A systematic search of PubMed for previous studies on the use of paracetamol dosage in preterm infants yielded 13 studies consisting of 2 randomized clinical trials comparing oral paracetamol and oral ibuprofen,16,17 and 11 case series using oral or intravenous paracetamol.[5-15] For case series using intravenous paracetamol, the proportion of successful PDA closure was between 75 and 100%.12-15 Our design was similar, but we had a larger sample size compared to previous case series. The proportion of successful PDA closure was lower at 65.5%, than in the four previous case series.

Previous studies had varied indications for administering intravenous paracetamol. Oncel et al. used intravenous paracetamol for 10 cases who were contraindicated for oral therapy and had no history of COX-inhibitor use. PDA closure occurred in 7 cases after the first intervention, and in 3 cases after the second intervention.13 One child died, but no liver toxicity was found. However, Terrin et al. gave intravenous paracetamol to 8 cases with contraindication of COX-inhibitors. Six cases had PDA closure after the intervention.[14]

El-Kuffash et al. used intravenous paracetamol for 9 cases, consisting of 4 cases with ibuprofen treatment failure and 5 cases with contraindication of COX-inhibitors. After intervention, 5 cases had PDA closure and 3 cases had significantly decreased duct diameter. Two cases died, but no liver toxicity was found.[12] Moreover, in a study by Tekgunduz et al., intravenous paracetamol was given to 13 cases, consisting of 7 cases with contraindication for oral ibuprofen and 6 cases having side effects associated with oral ibuprofen administration. Ten cases had PDA closure, but 2 cases experienced reopening of the PDA.[15]

In this study, intravenous paracetamol was given to subjects who could not be given enteral nutrition. In addition, intravenous preparations of ibuprofen and indomethacin were not yet available in Indonesia. Twenty-nine (58.8%) preterm infants experienced closure of PDA after the first intervention, however, 4 cases died due to severe sepsis and multiple organ system failure. Four babies experienced closure of PDA after the second intervention. After the follow up at 14 days of life, 19 (64.5%) infants experienced PDA closure, and one case had reopening of the PDA.

In previous studies, the PDA diameter significantly decreased after intravenous paracetamol administration for 3 days.[12-15] We also found a significant difference of PDA diameter before and after the intervention. Based on this study and previous studies, intravenous paracetamol could be used as an alternative treatment for PDA closure in preterm infants, especially in cases contraindicated for ibuprofen and indomethacin. No significant difference in duct diameter was observed after the second

intervention and follow up at chronological age of 14 days. As such, we think that there would be no benefit for administering a third intervention in cases with treatment failure after the second intervention. Hence, if treatment failure persists after the second intervention, we suggest performing a PDA ligation.

As a result of the left-to-right shunt, hemodynamically significant PDAs in preterm infants increase the risk of comorbidities associated with prematurity.[1,18] During the study, we found one case of gastrointestinal bleeding and 3 cases of grade III/IV IVH, but our results do not explain the relationship between intervention with intravenous paracetamol and such comorbidities. We continued with the intervention because no contraindication for intravenous paracetamol existed. Although we did not examine plasma paracetamol levels, similar to previous studies we found no cases of liver toxicity or increased AST and ALT levels.

A limitation of this study was that the before-and-after design does not prove a causal relationship between the administration of intravenous paracetamol or other management and PDA closure. Subjects also received supportive therapy that might have affected the closing process of the PDA. We also cannot explain the mechanism of intravenous paracetamol in inhibiting PGE2 synthesis, as we did not measure plasma prostaglandin levels. Despite these limitations, a before-and-after study design is a practical choice for the evaluation of the effectiveness of a complex intervention, and it is commonly used in clinical practice when a randomized controlled trial is not feasible.

In conclusion, intravenous paracetamol is quite effective as an alternative treatment in the closure of PDA in preterm infants, especially in preterm infants with feeding intolerance or when oral therapy is contraindicated.

Conflict of interest

None declared.

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