Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.62, No.2(2022). p.86-90; DOI: 10.14238/pi62.2.2022.86-90

Original Article

Factors contributing to successful patent ductus arteriosus closure with first pharmacological course

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Abstract

Background Successful closure of patent ductus arteriosus (PDA) with ibuprofen or paracetamol as the first-line treatment has been reported, but little is known about factors affecting the closure rate.
Objective To identify the closure success rate and contributing factors affecting a first course of pharmacological treatment in neonates with PDA.
Methods A retrospective study was conducted in infants with isolated PDA treated with either ibuprofen or paracetamol and admitted to our neonatal care unit from January 2017 until June 2020. Included infants had PDA on echocardiography and received ibuprofen or paracetamol therapy as the closure treatment. Oral ibuprofen was given at 10 mg/kg on first day, then 5 mg/kg on the 2nd and 3rd days; while paracetamol was given intravenously 15 mg/kg every 6 hours for 3 days. Echocardiographic evaluation was performed 3 days after first course of treatment.
Results In total, 20 of 33 (60.6%) infants achieved PDA closure with the first course of treatment. Earlier age at the start of the first course of treatment (PR 7.7; 95%CI 1.2 to 47.7; P=0.035) and normal birth weight (PR 13.3; 95%CI 2.4 to 72.4; P=0.001) were significant factors contributing to PDA closure. However, PDA size did not affect closure rate (PR 2.0; 95%CI 0.4 to 8.5; P=0.46).
Conclusion Pharmacological treatment seems to have a good success rate for PDA closure, with significant positive associations with earlier age at start of treatment and normal birth weight. **[Paediatr Indones. 2022;62:86-90; DOI: 10.14238/pi62.1.2022.86-90**].

Keywords: *patent ductus arteriosus; first course ibuprofen or paracetamol; successful closure*

Management options for PDA in infants are conservative monitoring, medical treatment, or surgical ligation, depending on the hemodynamic significance of the shunt and associated comorbidities.[1] Standard medical therapy for PDA closure mainly involves either indomethacin or ibuprofen. Both are successful in promoting ductal closure in 70-80% of cases.[2] In a study of preterm infants, closure rates for the first course of ibuprofen were more successful compared to second or third courses, with success rates of 66%, 56%, and 55%, respectively. Late start of the first course of ibuprofen was a predictive factor for increased need of a second course.[3] The other NSAID that showed satisfactory results for PDA closure was paracetamol,[4] with a success rate of 61.7% for the first course.[5] A randomized controlled trial noted PDA closure rates of 77.14% after paracetamol and 71.43% after oral ibuprofen. Oral ibuprofen and paracetamol had the same efficacy and safety.[6,7]

Factors associated with paracetamol effectiveness on PDA closure were ductal diameter, birth weight, gestational age, and postnatal age at the start of the treatment.[8] A retrospective study analyzed efficacy of the first course of ibuprofen and found a significant relationship between infant birth weight and PDA closure.[7] In Sanglah Hospital, Bali, no success rate

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Submitted May 9, 2021. Accepted March 4, 2022.

information is available on first courses of paracetamol or ibuprofen and PDA closure in neonates. As such, we aimed to assess the success rate of first paracetamol and ibuprofen courses and associated factors.

Methods

This retrospective, analytical research study was carried out in the neonatal care unit at Sanglah General Hospital, Bali, between January 2017 and June 2020. Subjects were infants with isolated PDA according to echocardiography results found by pediatric cardiologists and treated with paracetamol or ibuprofen for 3 days. Oral ibuprofen doses were 10 mg/kg on the first day and 5mg/kg on the second and third days; intravenous paracetamol doses were 15 mg/kg every 6 hours for 3 days. Echocardiographic evaluations were performed three days after first course of treatment. Infants with incomplete first courses or no echocardiographic evaluation after the first course were excluded. Complete closure was defined as closed PDA according to echocardiography results. Characteristics of subjects such as age at the start of the first course, birth weight, gestational age, PDA size, pharmacotherapy, and comorbidities, either related to or independent of PDA, were recorded.

The minimum required sample size as calculated by rule of thumb, which uses 10 times the number of variables, resulted in 30, because we used three variables (age at start of treatment, PDA size, birth weight). Patent ductus arteriosus were diagnosed by echocardiography performed by a pediatric cardiologist at Sanglah Hospital; PDA size was classified into three groups: (1) small PDA (<1.5 mm), (2) moderate PDA (1.5-2.5 mm), or large PDA (≥2.5 mm) and birth weight was classified into two groups; (1) normal (≥ 2500 gram) and low (< 2500 gram). Cases were included by consecutive sampling until the sample size requirement was fulfilled.

Descriptive data were presented with numerical and categorical data. Numerical data were presented as means if it was normally distributed and median if it was not normally distributed. Categorical data were presented as number of cases. Fisher's exact test was used to compare the age at the start of the first course and PDA size with PDA closure; Chi-square test was used to analyze birth weight and PDA closure. Computerized statistical analysis was performed to calculate prevalence ratio (PR). Results with P values <0.05 were considered to be statistically significant, with 95% confidence intervals (CI). All statistical analyses were performed using *SPSS version 22* software. This study was approved by the Ethics Committee of the University of Udayana, Faculty of Medicine.

Results

A total 33 cases of PDA were included, of whom 20 subjects (60.6%) had successful PDA closure after administration of ibuprofen or paracetamol for 3 days. The characteristics of the study subjects are shown in **Table 1**.

Factors potentially associated with successful PDA closure after the first course of ibuprofen or paracetamol were investigated. Age of <3 days at the start of the first treatment course and normal birth weight were significant factors contributing to PDA closure (**Table 2**).

Table 1. Demographic characteristics of subjects

Characteristics	PDA closure	
	Yes (n=20)	No (n=13)
Median age at the start of the first course (range), days	1 (0-5)	3 (0-14)
Mean birth weight (SD), kg	2.8 (0.57)	1.8 (0.14)
Gestational age, n		
Full term	14	3
Preterm	6	10
PDA size, n		
Small	14	7
Moderate	3	4
Large	3	2
Pharmacotherapy, n		
Ibuprofen	18	10
Paracetamol	2	3
Comorbidities, n		
Yes	12	10
Neonatal pneumonia	6	3
Hyaline membrane disease	0	4
Neonatal sepsis	1	2
Congenital rubella syndrome	3	0
Others	2	1
No	8	3

Others: neonatal meningitis, multiple congenital anomalies, pulmonary hypertension

Table 2. Analysis of successful closure of PDA to age at the start of first course, birth weight, and PDA size

Variables	PDA closure		PR	95% CI	P value
	Yes (n=20)	No (n=13)			
Age at the start of the first course					
≤ 3 days	18	7	7.7	1.2 to 47.7	0.035†
> 3 days	2	6			
Birth weight					
Normal	16	3	13.3	2.4 to 72.4	0.001‡
Low	4	10			
PDA size					
Small	14	7	2.0	0.4 to 8.5	0.46†
Moderate-large	6	6			

†Fisher's exact test; ‡Chi-square test

Discussion

Patent ductus arteriosus is a frequent complication in neonates, especially preterm infants. The PDA accounts for 5-10% of all congenital heart disease in term infants, while 60-70% of preterm infants receive medical or surgical therapy for PDAs.[9] The ductus arteriosus closes spontaneously in most healthy term newborns during the first three days after birth.[10] Within 24-72 hours after a full-term birth, the DA (ductus arteriosus) closes as a result of increased oxygen tension as well as decreased circulating prostaglandins (PGE_2) and prostacyclins (PGI_2). As oxygen tension increases, smooth muscle voltage-dependent potassium channels are inhibited, leading to an influx of calcium which contributes to ductal constriction. This oxygen-induced constriction fails in preterm infants, potentially due to the immaturity of oxygen-sensing receptors. Circulating levels of PGE_2 and PGI_2 are decreased as a result of increased metabolism in the newly functioning lung, as well as removal of the placental source. The decreased circulating levels of these potent vasodilators allow the DA to constrict.[11]

Prostaglandins play a major role in patency of the ductus, and cyclooxygenase (COX) inhibitors are conventionally used to induce its closure. Non-selective COX inhibitors indicated for PDA closure are indomethacin and ibuprofen, both of which are equally effective in PDA closure. Administration of ibuprofen may be associated with decreased incidence of adverse events, particularly renal toxicity. Furthermore, ibuprofen may also have a less significant impact on cerebral blood flow and mesenteric blood flow, and thus may be associated with fewer effects on neurologic development and incidence of necrotizing enterocolitis.[10]

In our study, PDA closure occurred in 60.6% of subjects treated with either ibuprofen or paracetamol. Similarly, a randomized controlled trial in preterm infants reported PDA closure rates of 77.14% after ibuprofen, and 71.43% after paracetamol.[7] Another cohort study in preterm infants with a gestational age of <32 weeks also had similar results, with first, second, and third course success rate of 66, 56, and 55%, respectively.[3] In contrast, a study of preterm infants with very low birth weight (<1,000 grams) found closure rates after the first course of ibuprofen to be 45%.[12] The differences in closure rates were probably because their study population was limited to preterm infants with very low birth weight, while our study was not limited to preterm infants.

Several factors have been associated with a higher closure rate after pharmacological treatment, including earlier age at the start of ibuprofen or paracetamol, normal birth weight and smaller ductal diameter.[12] Closure rate after the first course of ibuprofen significantly increased if treatment was started prior to postnatal day 5.3 The higher closure rate after the first course of ibuprofen if started at early postnatal age, may have been due to the pharmacokinetic characteristics of ibuprofen. Ibuprofen is metabolized by the cytochrome P450 complex, especially the CYP2C9 and CYP2C8 enzymes. Directly after birth these enzymes are absent in the serum, and during the first week of life they increase to 33% of the adult serum level, independent of gestational age. Therefore, the available concentration of ibuprofen decreases during the first week of life due to increased metabolism, resulting in less bioavailability

for closure of the ductus.[5] The clearance of ibuprofen increased with postnatal age, when the same dose of ibuprofen was administered to all neonates, efficacy will decrease with age.[13]

The beneficial effect of paracetamol in PDA closure is mediated through the ability of paracetamol to inhibit in vivo prostaglandin synthesis.[17] Paracetamol does not access the active site of the the cyclooxygenase (COX) subunit of prostaglandin H synthase, but rather acts on the peroxidase (POX) segment of prostaglandin H synthase.[18,19] Intravenous paracetamol is usually given to subjects who cannot be given enteral nutrition.[4] Paracetamol and ibuprofen have similar PDA closure rates.[5] In our study, 5 subjects used intravenous paracetamol, 3 of whom failed as first course therapy.

In our study, normal birth weight was also significantly associated with successful PDA closure. A similar result was found in a previous retrospective study, with a failure rate of 55% for the first course of ibuprofen, which occurred in 62% of infants born before 27 weeks of gestation. Since low birth weight and premature infants have immature organ systems, they are more susceptible to pharmacological interactions.[14,15]

Two retrospective studies showed that PDA size was significantly smaller in the successful closure group than in the failed closure group, after receiving the first course of medical treatment.[15,16] In our study, we found that smaller PDA size was not associated significant with successful PDA closure. Since the mechanism of PDA closure by ibuprofen or paracetamol is by initiating functional closure, when a PDA is too large, complete functional closure of the ductal lumen via extensive muscular constriction cannot be achieved with the therapy.[16]

The presence of hemodynamic disorders can influence the success rate of PDA closure.20 In our study, 22 of 33 subjects had other comorbidities that could impact their hemodynamics. Comorbidities in our subjects were neonatal pneumonia, hyaline membrane disease, congenital rubella syndrome, neonatal sepsis, neonatal meningitis, multiple congenital anomalies, and pulmonary hypertension. We did not analyze PDA closure success and these conditions.

Our study had several limitations, such as small sample size and not limiting the sample to preterm infants. Subsequent studies are needed with a larger sample size so that more variables can be studied, and use of a population of preterm infants only.

In conclusion, pharmacological treatment seems to have a good success rate and is associated with earlier age at start of treatment and normal birth weight.

Conflict of interest

None declared.

Funding acknowledgements

The authors received no specific grants from any funding agency in the public, commercial, or non-for-profit sectors.

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