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Intravenous Paracetamol and Patent Ductus Arteriosus Closure

Herlina Dimiati[1*], Dora Darussalam[2], Isra Firmansyah[2]

1. Pediatric Cardiology Division, Department of Child Health, Medical School, Syiah Kuala University, Zainoel Abidin Hospital, Banda Aceh, Indonesia
2. Neonatology Division, Department of Child Health, Medical School, Syiah Kuala University, Zainoel Abidin Hospital, Banda Aceh, Indonesia

ABSTRACT

Background: Standard medical treatments for patent ductus arteriosus (PDA) closure are, including indomethacin/ibuprofen and surgical ligation. Nowadays, a new strategy to close PDA is the use of paracetamol. The present study aimed to describe the use of intravenous (IV) paracetamol for PDA closure in neonates who present a contraindication to ibuprofen or ibuprofen failure with no possibility to perform surgical ligation due to major instability.

Methods: The present study was conducted from January to December 2017 in the neonatal intensive care unit of Dr. Zainoel Abidin Hospital and Harapan Bunda Hospital, Banda Aceh, Indonesia, on neonates with hemodynamic significant PDA (hsPDA). All the subjects received IV paracetamol (15 mg/kg every 6 h) for 3 days. Thereafter, the ductus was evaluated by echocardiography on the 5th day after the regiment.

Results: A total of 72 neonates were diagnosed with hsPDA and their average of gestational age was 34.26 weeks and their average of birth weight was 1945.69 g for 39 (54.2%) female neonates, 33 (45.8%) male neonates, 45 (62.5%) premature infants, and 27 (37.5%) full-term infants. About 26 (36.1%) infants had a closed PDAs on the 5th days of evaluation, 11 (15.3%) infants had regiment twice for closed PDA at the 10th days of evaluation, and 35 (48.6%) neonates had more closed PDA after three or four regiments. Successful closure with paracetamol was achieved in 51(70.8%) neonates, while 21 (29.2%) neonates failed the PDA closure.

Conclusion: Based on the findings of the present study, IV paracetamol appears to be reasonably effective for PDA closure in both preterm and term infants. This should be the first-line of therapy choice when there are contraindications for the treatment with ibuprofen.

Keywords: Effective choice, Paracetamol, Patent ductus arteriosus

Introduction

Ductus arteriosus (DA) is a heart condition that is frequently observed in the first few weeks or months after birth. It is characterized by the presence of normal fetal connections between the aorta and the pulmonary arteries, which allows oxygen-rich (red) blood to travel throughout the body to recirculate through the lungs. Closure of the DA after birth is critical for circulation adaptation to extrauterine life. In healthy full-term newborns, DA generally undergoes functional closure within 24-72 h of life (1, 2). Prolonged conditions of patent ductus arteriosus (PDAs) in preterms can be associated with vital complications, such as severe respiratory distress syndrome, prolonged need for assisted ventilation, pulmonary hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, renal function damage, intra-ventricular hemorrhage, and periventricular leukomalacia. To prevent such complications, the practice of DA closure is common and it is performed pharmacologically; however, in case of drug failure or contraindication, surgery is needed (1-4).

Despite years of research and clinical experience on PDA management, there are still many unresolved issues about its evaluation and

* *Corresponding author*: Herlina Dimiati, Pediatric Cardiology Division, Department of Child Health, Medical School, Syiah Kuala University, Zainoel Abidin Hospital, Banda Aceh, Indonesia. Tel: 065143325; Email: herlinadimiati@unsyiah.ac.id, herlinadimiati@yahoo.com

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treatment. The consequent heterogeneity of clinical practices in different centers still remains, particularly regarding the timing and modality of the intervention. The available strategies vary between prophylactic treatment and early or delayed therapy. Pharmacological closure with nonsteroidal anti-inflammatory drugs (NSAIDs), mainly ibuprofen and indomethacin, is currently the standard care for PDA closure in preterm infants. However, NSAIDs are not effective for around 25-30% of patients and they can cause side effects, such as transient renal function impairment, diminished platelet aggregation, hyperbilirubinemia, gastrointestinal bleeding, and perforation (3, 4). Recently, there is a growing interest in the usage of paracetamol for PDA closure, and it has been suggested as an alternative to manage PDA. Finding the optimal pharmacological treatment for PDA closure in very low birth weight (BW) neonates continues to remain challenging. The role of paracetamol, an inhibitor of the peroxidase component of prostaglandin-H2 synthesized, has been proposed for the treatment of PDA (4, 5).

Hammerman et al. were the first to report the use of paracetamol for PDA closure (5). Since then, many studies have reported similar efficiency of paracetamol over cyclooxygenase (COX) inhibitors for PDA closure with the occurrence of lower adverse events[6]. Many studies reported the alternative treatment for closing the ductus (6-8).

Since 2014, paracetamol has been used as a standard practice at Dr. Zainoel Abidin and Harapan Bunda hospitals for PDA closure. It has also been found in standard operational procedures at the neonatal intensive care unit (NICU); therefore, there have been no studies on the effectiveness of this drug in PDA closure. As a result, the present study aimed to present the authors' experience related to intravenous (IV) paracetamol for closing PDA in premature or mature neonates suffering from contraindications to ibuprofen, ibuprofen failure and intolerance.

Methods

The present study was approved by the Ethics Committee of Medical Faculty, Syiah Kuala University, Banda Aceh, Indonesia. The study was performed in two hospitals in Banda Aceh, namely, Dr. Zainoel Abidin Hospital and Harapan Bunda Hospital from January to December 2017. Echocardiography, hemodynamically significant of PDA (hsPDA), were performed on the subjects who met the inclusion criteria. The echocardiography criteria of hsPDA were a ductal diameter ≥ 1.5 mm, a left atrium to aortic root ratio > 1.5, and diastolic aortic retrograde flow. Bi-dimensional color Doppler echocardiography with GE Vivid Healthcare multi-frequency 7 MHz sector probe was used. All the preterm or term newborns received paracetamol 15 mg/kg IV administration every 6 h for 3 consecutive days, the re-evaluation of PDA closure was carried out on the 5th day. If the ductus closure was confirmed by echocardiography, the treatment was discontinued, and if PDA was not closed, the regiment repeated with the same dose for 3 consecutive days. This repetition of the regiment can only be performed four times. The failure category of a PDA closure is that if it repeats up to four times regiment, the PDA does not close.

Demographic features (e.g., gestational age (GA), gender, BW, height, Apgar score, delivery mode, antenatal steroids, MgSO4, age/days of treatment, primary reason to use paracetamol, main outcome, adverse events, surgery, and invasive ventilation), times of treatment, response to treatment before and after 24 h of paracetamol treatment, and liver function tests were performed on all patients. In all cases, written informed consent was obtained.

The collected data were analyzed in SPSS and a descriptive analysis was carried out to elaborate subjects' demographics and clinical data. A p-value of ≤ 0.05 was considered to be statistically significant.

Results

Between January and December 2017, there was a total of 72 preterm and full-term neonates who had PDA with a GA of 28 and 40 weeks (average 34.26 weeks), an average of BW was 1945.69 g ranging from 870 to 4,000 g. A total of 45 (62.5%) neonates were preterm and 27 (37.5%) were full-terms. Table 1 describes the demographic characteristic among neonates who received IV paracetamol.

Due to food intolerance and clinical instability of the patients, IV paracetamol was given after obtaining an informed consent signature. Complete closure was observed in 51(70.8%) neonates. Out of the 27 term-infants, the success of the PDA closure was more than 50% (n=15). The average of postnatal age at the first IV paracetamol dose was 2.7 days ranging from 1 to 4 days.

Bivariate analysis showed that ductal closure had significant relationships with GA, BW, PDA diameter, days of treatment, and times of regiment (Table 2, 3).

Table 1. Participants' characteristics

Characteristics	Preterm neonates N (%)	Term neonates N (%)
Gender		
Girls	26 (57.8)	13 (48.1)
Boys	19 (42.2)	14 (51.9)
GA average (weeks)	32.3	37.5
BW average (grams)	1.022	1.666
PDA average size (mm)	5.92	8.28
Average days of treatment	3	2.14
Regiment		
One time	22 (48.9)	4 (14.8)
Twice	8 (17.8)	3 (11.1)
Three times	3 (6.7)	5 (18.5)
Four times	12 (26.7)	15 (55.6)
Close of PDA	36 (80)	15 (55.6)
Fail Close of PDA	9 (20)	12 (44.4)

PDA: Patent ductus arteriosus
GA: Gestational age
BW: Birth weight

Table 2. Bivariate analysis of ductal closure and gestational age, birth weight, patent ductus arteriosus diameter, days of treatment, and times of regiment

Variable	P-values
GA	0.015
BW	0.002
Size of PDA	0.020
Days of treatment	0.001
Times of regiment	0.000

GA: Gestational Age, BW: Birth Weight, PDA: Patent ductus arteriosus

Table 3. Multivariate analysis of variables to predict patent ductus arteriosus closure

	SE	P-value	R
GA	0.036	0.008	2.840
BW	0.000	0.001	3.650
Size of PDA	0.018	0.010	2.740
Days of treatment	0.100	0.000	3.930
Times of regiment	0.044	0.000	6.170

GA: Gestational Age, BW: Birth Weight, PDA: Patent ductus arteriosus, SE: Standard error, R: regression

Discussion

Recently, oral or IV administration of paracetamol (acetaminophen) has gained attention in PDA treatment. Although the way that paracetamol acts for closing PDA remains unclear, it is known that it inhibits prostaglandin synthesized (4-6). The role of paracetamol as an alternative treatment for the closure of hsPDA has gained attention in recent years because of its superior safety profile in comparison to the COX inhibitors. Alternatively, paracetamol has been proposed to inhibit a central isoform of COX3 selectively; however, the existence of a functional human COX3 has been questioned (5-8). Moreover, the paracetamol inhibits prostaglandin synthesized activity, although its precise mechanism of action remains controversial. Theoretically, the differences would permit peroxidase inhibition to become effective in conditions where COX inhibition is less active or hypothetically, making it suitable for treatment in a PDA environment (6-10).

Hammerman et al. were the first who performed several case reports on premature infants receiving paracetamol that reached ductal closure (5). Since then, 24 cases have been reported, and six randomized control trials (RCTs) showed that paracetamol utility for ductal closure has similar results to ibuprofen/indomethacin, with fewer adverse events (1, 5). A study by Oncel et al. used paracetamol in 10 premature infants under 30 weeks of GA with 100% effectiveness. However, other researchers did not achieve the same striking results (7, 8). The most common dosage is 15 mg/k/dose/6qh. Sinha R et al. used oral paracetamol; however, the result for closed ductal was not satisfactory (10). In the current study, all newborns had feeding problems; therefore, paracetamol was given 15 mg/k/dose/q6h intravenously. A lower average of ductal closure has been reported in the present study which did not separate preterm and full-term neonates. To the best of the authors' knowledge, no research has studied the effectiveness of paracetamol for the closure of PDA. Studies conducted by Roofthooft DW et al. and Tekgündüz KS et al. reported satisfactory results in the closing ductal of paracetamol administration (11, 12). A recent report has reinforced the long-term neurodevelopmental safety of paracetamol in comparison to ibuprofen

in 80 preterm neonates (13). Considering the published equivocal reports and the promise offered by paracetamol as a safer alternative, randomized, active-controlled, masked, and non-inferiority trial, in the current study, no subject had a neurodevelopmental problem after a 6-month evaluation.

In the present study, all neonates with hsPDA received treatment with IV paracetamol because of this treatment was included in the standard operating procedures at the NICU. The result of the current research showed that there were many cases that failed to close the PDA in full-term infants, compared to preterm infants (n=12, 44.4%). There were several reasons for why a PDA becomes unresponsive to the administration of non-steroidal anti-inflammatory drugs (NSAIDs). The inflammatory process in the wall of a DA occurs soon after birth. It is associated with the influx of monocytes or macrophages into the walls of the DA which later induces the prostaglandin and Nitride-Oxides (NO)- independent cytokines-mediated vasodilation (14).

Preterm neonates obtained good results with the success of PDA closure at 36 (80%), 22 (48.9%) out of 36 neonates only got one regiment, while 15 (55.6%) term neonates succeeded to close the PDA by receiving four times of regiment. These results indicate that although paracetamol can affect the closure of PDA for in term neonates, this drug is more successful in preterm subjects.

In addition, the success of PDA closure also depended on the infant's weight, GA, size of PDA, and on the day of drug administration. The only side-effect was a transient elevation in liver enzymes, and only four preterm subjects had this condition and did not require therapy.

The patients experienced oral feeding intolerance; therefore, the researchers used the IV paracetamol route. In researchers' view, the oral route may not be the optimal choice for the subjects. For these patients, intestinal immaturity along with oral feeding-intolerance could lead to unpredictable and possibly too low intestinal drug absorption.

The current research was a single-center study involving a relatively small sample size. Nevertheless, to the best of the researchers' knowledge, the present research was the first study which was performed at the authors' hospitals in Banda Aceh, Indonesia. Due to the success rate of PDA closure with IV paracetamol, its use has now been approved by the Hospital's Medical Committee.

Conclusion

The obtained results highlighted that paracetamol could become not only an alternative treatment in closing PDA but also a treatment of choice in several scenarios. Nevertheless, small sample size was one of the main limitations of the present study. Further studies are required to determine the long-term consequences of using paracetamol for closing PDA, answer important questions about the optimal dose, the best route of administration, safety, and the implications for term newborns.

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None.

Conflicts of interests

The authors declare that there are no conflicts of interest regarding the publication of the present research.

References

1. Agarwal R, Deorari AK, Paul VK. Patent ductus arteriosus in preterm neonates. Indian J Pediatr. 2008; 75(3):277.
2. Allegaert K, Anderson B, Simons S, van Overmeire B. Paracetamol to induce ductus arteriosus closure: is it valid? Arch Dis Child. 2013; 98(6):462-6.
3. Brunner B, Hoeck M, Schermer E, Streif W, Kiechl-Kohlendorfer U. Patent ductus arteriosus low platelets, cyclooxygenase inhibitors and intraventricular hemorrhage in very low birth weight preterm infants. J Pediatr. 2013; 163(1):23-8.
4. Weisz DE, More K, McNamara PJ, Shah PS. PDA ligation and health outcomes: a meta-analysis. Pediatrics. 2014; 133(4):e1024-46.
5. Hammerman C, Bin-Nun A, Markovitch E, Schimmel MS, Kaplan M, Fink D. Ductal closure with paracetamol: a surprising new approach to patent ductus arteriosus treatment. Pediatrics. 2011; 128(6):e1618-21.
6. Dani C, Poggi CH, Mosca F, Schena F, Lista G, Ramenghi L, et al. Efficacy and safety of IV paracetamol in comparison to ibuprofen for the treatment of patent ductus arteriosus in preterm infants: study protocol for a randomized control trial. Trials. 2016; 17:182.
7. El-Khuffash A, Amish J, Corcoran D, Shah P, Hooper CH, Brown N, et al. Efficacy of paracetamol on patent ductus arteriosus closure may be dose dependent: evidence from human and murine studies. Pediatr Res. 2014; 76(3):238-44.
8. Oncel MY, Yurttutan S, Uras N, Altug N, Ozdemir R, Ekmen S, et al. An alternative drug (paracetamol) in the management of patent ductus arteriosus in ibuprofen-resistant or contraindicated preterm infants. Arch Dis Child Fetal Neonatal Ed. 2013; 98(1):F94.

9. Oncel MY, Yurttutan S, Degirmencioglu H, Uras N, Altug N, Erdeve O, et al. IV paracetamol treatment in the management of patent ductus arteriosus in extremely low birth weight infants. Neonatology. 2013; 103(3):166-9.
10. Sinha R, Negi V, Dalal SS. An interesting observation of PDA closure with oral paracetamol in preterm neonates. J Clin Neonatol. 2013; 2(1):30-2.
11. Roofthooft DW, van Beynum IM, Helbing WA, Reiss IK, Simons SH. Paracetamol for ductus arteriosus closure: not always a success story. Concerning the article by M.Y. Oncel et al: IV paracetamol treatment in the management of patent ductus arteriosus in extremely low birth weight infants [Neonatology 2013;103:166-169]. Neonatology. 2013; 104(3):170.
12. Tekgündüz KS, Ceviz N, Caner I, Olgun H, Demirelli Y, Yolcu C, et al. IV paracetamol with a lower dose is also effective for the treatment of patent ductus arteriosus in pre-term infants. Cardiol Young. 2015; 25(6):1060-4.
13. Oncel MY, Eras Z, Uras N, Canpolat FE, Erdeve O, Oguz SS. Neurodevelopmental outcomes of preterm infants treated with oral paracetamol versus ibuprofen for patent ductus arteriosus. Am J Perinatol. 2017; 34(12):1185-9.
14. Hermes-DeSantis ER, Clyman RI. Patent ductus arteriosus: pathophysiology and management. J Perinatol. 2006; 26(Suppl 1):14-8.