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The Prevalence and Success Factor of Ibuprofen and Paracetamol Administration for Neonates with Patent Ductus Arteriosus at RSUD Dr. Soetomo

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Abstract

Background: Four thousand neonates with Persisten Ductus Arteriosus every year in Indonesia. There are two treatment options to treat Persistent Ductus Arteriosus, they are surgery and pharmacological therapy. Ibuprofen and paracetamol can be used as pharmacological therapy for Persistent Ductus Arteriosus with minimal side effects.

Objective: To analyze the prevalence and success factors in giving ibuprofen and paracetamol in neonates with persistent ductus arteriosus.

Method: This research is an observational analytic research with cross-sectional method. The determination of the research sample uses a total sampling technique by taking all members of the population in accordance with the conditionsfrom January, 2016 to March , 2020. Bivariate analysis was perform using the Spearman rank test with 95% confidence interval (α=0.05).

Result: From 51 samples that met the inclusion criterias, it was found that the most criterias were male (66.67%), normal birth weight (60.78%), aterm (76.48%), moderate defect size before being administrated pharmacological therapy (47.06%), pharmacological therapy using paracetamol (88.24%), atrial septal defect in the cardiac comorbidities category (21.74%) and hyperbilirubinemia in the non-cardiac comorbidities category (13.04%). The majority of lumen defects in neonates were closed completely after being administrated pharmacological therapy (72.55%). Statistical test results of spearman rank showed that no significant relationship between birth weight and pharmacological therapy in RSUD Dr. Soetomo. There was a significant relationship between gestation and pharmacological therapy (p = 0.000; r = -0.495; r2 = 0.237, 95% CI). There was a significant relationship between the size of the ductus arteriosus defect before therapy and pharmacological therapy (p = 0.001; r = -0.435; r2 = 0.211, 95% CI).

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Conclusion: The success factors in administrating ibuprofen and paracetamol for neonates with persistent ductus arteriosus in RSUD dr. Soetomo from January 1, 2016 to March 3, 2020 were affected by gestation period and size of the ductus arteriosus defect prior to pharmacological therapy.

Keywords: Patent Ductus Arteriosus; neonate; ductus arteriosus.

Introduction

Four million neonates die due to asphyxia every year. Indonesia is in the fifth place of neonatal asphyxia mortality rate in ASEAN countries in 2011 of 35 per 1000.[1] The high incidence of asphyxia in newborns can cause complications such asthe failure of the ductus arteriosus to be closed in neonates. Asphyxia that causes persistent ductus arteriosus can be caused by lung function that has not developed optimally and birth weight is underweight.[2] Besides caused by lungs that are not yet optimal, Reactive Oxygen Species (ROS) causes high levels of prostaglandins (PG), nitrogen monoxide (NO), and decreased sensitivity of calcium and oxygen to muscle blood vessels. Thus, it causes the ductus arteriosus do not close in neonates.[3]

The treatment of PDA (Patent Ductus Arterious) continues to develop until now. Initially, the management of PDA was conducted in an invasive manner through surgery.[4] However, surgery requires a lot of money and not all hospital can provide it. It is considered ineffective to treat small to moderate PDA. Along with the development of technology and knowledge in the medical field, surgical or non-pharmacological therapy is only carried out if a large ductus arteriosus is found, it does not respond to the use of at least two therapeutic drugs, patients are on ventilators and patients with high oxygen needs. Meanwhile, pharmacological therapy can be performed by administering indomethacin (non-selective COX inhibitor) as one of the nonsteroidal anti-inflammatory drugs (NSAIDs). Indomethacin can cause side effects such as impaired kidney function, gastrointestinal bleeding, and impaired cerebral blood flow.[4] Therefore, other NSAIDs are needed. They can be used for DAP closure but with low side effects. Ibuprofen and paracetamol can be used as closure therapy for PDA with minimal side effects.[6]

The use of ibuprofen for Persistent Ductus Arteriosus has received approval from the FDA (Food and Drug Administration) since 2009.[7] The effectiveness of ibuprofen as a therapeutic drug in PDA is around 60% to 80%.[8] 30% of PDA patients have closed the lumen of their ductus arteriosus in 24 hours of being administrated ibuprofen therapy.[9] Paracetamol is used when the patient is intolerant to ibuprofen or they has conditions that contraindicate the use of ibuprofen.[10] The success rate of using paracetamol in closing the ductus arteriosus is 83.3% to 100%.[11] Ductus Arteriosus successfully closes using paracetamol at 55/59 or about 93 % of PDA patients.[6]

The success of pharmacological therapy on Persistent Ductus Arteriosus using ibuprofen and paracetamol can be affected by several factors. Therefore, researchers are encouraged to conduct research with the main objective of obtaining information about the characteristics of neonates with Persistent Ductus Arteriosus and the results of pharmacological therapy and the factors that influence the success of pharmacological therapy in Dr. Soetomo for the period of January 1, 2016 to March 3, 2020.

Methods

This research was a type of retrospective analytic observational study with a cross-sectional study design using secondary data in the form of medical records. This research was conducted by analyzing data obtained from the medical records of persistent ductus arteriosus neonates in the pediatric inpatient room dr. Soetomo for the period of January 1, 2016 to March 3, 2020. The sample size used the total sampling technique with inclusion criteria, such as persistent ductus arteriosus neonates who needed pharmacological therapy to close the ductus arteriosus. The exclusion criteria were (1) persistent ductus arteriosus neonates who had incomplete medical records, (2) undergoing surgical therapy to close the ductus arteriosus, (3) the patient died during the pharmacological therapy of PDA. The data taken were gender, gestation period, birth weight, pharmacological therapy, defect size, results of therapy, comorbidities. The independent variables in this research were the type of pharmacological therapy selected, gestation period, birth weight, gender, and size of the ductus arteriosus defect before treatment. The dependent variable in this research was the success rate of pharmacological therapy in Persistent Ductus Arteriosus patients. Data processing was performed using SPSS version

26 software. Univariate analysis was conducted descriptively to determine the characteristics of the sample. Bivariate analysis to determine the relation between the independent variable and the dependent variable was conducted using the Spearman Rank analysis test with a 95% confidence level. Significance value of (p value) <0.05 was considered significant.

Results

From 125 neonates with persistent ductus arteriosus who were hospitalized at Dr. Soetomo from January 1, 2016 to March 3, 2020, it was obtained 51 complete medical records and met the criteria for research sample.

Tabel 1: Characteristics(n=51)

Characteristics	n	%
Gender		
Male	34	66,67
Female	17	33,33
Birth Weight		
LBW	18	35,3
NBW	31	60,78
HBW	2	3,92
Gestational Age		
Preterm	9	17,64
Aterm	39	76,48
Posterm	3	5,88
Size of Ductus Arteriosus Before Pharmacology Therapy		
Large	8	15,69
Moderate	24	47,06
Small	19	37,25
Size of Ductus Arteriosus After Pharmacology Therapy		
Large	2	3,92
Moderate	5	9,80
Small	10	19,61
Closed	34	66,67
Pharmacology Therapy		
Ibuprofen	6	11,76
Paracetamol	45	88,24

* LBW: Low Birth Weight (<2500 gram), NBW: Normal Birth Weight (2500-4000 gram), HBW : High Birth Weight (>4000 gram)

The characteristics of the sample in this researchis shown in Table 1. The majority of the samples were male (66.67%), birth weight was between 2500 - 4000 grams (60.78%), gestation period of 37-42 weeks (76.48%)), the size of the defect was moderate before being given pharmacological therapy (47.06%), the choice of pharmacological therapy using paracetamol (88.24%), the comorbid Atrial Septal Defect in the comorbid cardiac disease category (21.74%) and hyperbilirubinemia in category of non-cardiac comorbidities (13.04%).

Tabel 2: Comorbidities

	Comorbidities	%
Cardiac	Atrial Septal Defect	21,74
	Tricuspid Regurgitation	10,14%
	Dextrocardia	1,45%
	Mitral Valve Regurgitation	1,45
	Hipertensi Pulmonal	1,45
Non - Cardiac	Hyperbilirubinemia	13,04
	Septic	8,70
	Asphyxia	7,25
	Pnemonia	7,25
	Hypoglycemia	4,35

Table 2 shows the top five distributions of comorbidities in each category (cardiac comorbidities and non-cardiac comorbidities) in neonates with persistent ductus arteriosus. The percentage was obtained from 51 neonates. A neonate can have more than one comorbidity. The majority of neonates with PDA suffered from atrial septal defects in the cardiac comorbidities' category and hyperbilirubinemia in the non-cardiac comorbidities category.

Tabel 3: The Spearman's Rank Correlation Test Result

Spearman's Rank		p value	r	r2
Birth Weight	LBR	0,412	0,128	0,016
	NBR			
	HBR			
Gestation Age	Preterm	0,001	0,442	0,195
	Aterm			
	Posterm			
Size of Ductus Arteriosus	Small	0,001	0,459	0,211
	Moderate			
	Large			

* LBW: Low Birth Weight (<2500 gram), NBW: Normal Birth Weight (2500-4000 gram), HBW : High Birth Weight (>4000 gram)

The analysis result of the relation between birth weight and the success of therapy did not show a significant relation. It was evidenced by the significance value of the p value of 0.412 (p value (0.412)> α (0.05)). The coefficient of determination (r2) was 0,016. Thus, it can be stated that the effect of birth weight on the success of therapy in PDA in RSUD dr. Soetomo was 1.6% and the rest was affected by other factors.

With the results of statistical tests using the Spearman SPSS correlation method, the p value = 0.000 (p <0.05), it indicated that there was a significant relationship between gestation period and the success rate of pharmacological therapy in neonates with persistent ductus arteriosus. Spearman's rho correlation coefficient (r) was 0.495. It means that the level of closeness of the relation between gestation and the success of pharmacological therapy at Dr. Soetomo Hospital was in the moderate category (0.40 - 0.59). A positive sign means that the direction of the relation between the two variables was unidirectional. It means that the greater the gestation period, the greater the success of pharmacological therapy. The coefficient of determination (r2) was0.237. Furthermore, this value can be multiplied by 100% to convert it into a percentage. Thus, it can be stated that the effect of defect size on the success of therapy in PDA in RSUD dr. Soetomo was 23.7% and the rest was affected by other factors.

The results of the analysis of the relationship between the size of the ductus arteriosus lumen defect and the success of therapy using the SPSS correlation method were the significance value (p value) of 0.001. It means p value <α (0.05). Thus, it can be stated that there was a significant relation between the size of the lumen defect and the success of pharmacological therapy in RSUD dr. Soetomo. The correlation coefficient value of Spearman's rho (r) was -0.435. It means that the degree of closeness of the relation between the size of the lumen defect and the success of pharmacological therapy in RSUD Dr. Soetomo was in the medium category (0.40 - 0.59). The negative sign means that the direction of the relation between the two variables was opposite. Thus, the larger the defect size, the smaller the success of pharmacological therapy. The coefficient of determination (r2) was 0.211. next, this value could be multiplied by 100% to convert to a percentage. Therefore, it can be explained that the effect of defect size on the success of therapy in PDA in RSUD dr. Soetomo was 21.1% and the rest was affected by other factors.

Discussion

A. Sample Characteristic

From 51 persistent ductus arteriosus neonates in this research, it was found that a higher percentage of male babies (66.67%) than women was found. This result was not in accordance with the research conducted by James E. Dice. It showed that the incidence rate of neonatal PDA in females compared to males was 2: 1.[12] More PDA cases in males can be caused by fetuses of the female that have less prostaglandin synthase and greater prostaglandin dehydrogenase than males.[13]

The majority of PDA neonates were born with adequate birth weight of around 2500 - 4000 grams of 31 neonates (60.78%). The majority of subjects in this research were neonates with normal birth weight, because the majority of neonates who were born underweight would undergo further surgery to treat PDA. Thus, they would be included in the exclusion category in this research. The majority of neonates with sufficient birth weight with PDA would be given pharmacological therapy because the body organs were structurally and functionally mature. Thus, they were at low risk of experiencing metabolic and cardiovascular disorders.

The results of this research also showed that from a total of 51 neonates, the most samples were found in the group at term gestation (37 - 42 weeks) of 76.48%. This was not in accordance with other research stated that one third of neonates with PDA were neonates born prematurely.[14] Neonates with less gestational age would worsen the ability to absorb, distribute, metabolize and excrete drugs. Thus, in preterm neonates, the safety of both short and long-term pharmacological therapy was unclear because the resulting effect of increased indirect free and total bilirubin might increase the risk of developing bilirubin encephalopathy. Organ maturity that has been already perfect in term and posterm neonates, both structurally and functionally, had a low risk of experiencing metabolic and cardiovascular disorders.[15]

The use of ibuprofen therapy for Persistent Ductus Arteriosus patients has been researched since 2006 and received approval from the FDA (Food and Drug Administration) in 2009. Paracetamol can't be used as a first-line drug for PDA.[7] Yet, based on research conducted by Dang et al., Paracetamol can be used as one of the main therapies chosen to close

Ductus Arteriosus in neonates, even when Ductus Arteriosus lumen reopening occurs, paracetamol is still proven to be effective.[16] Based on the results of the research, it was found that 6 neonates received ibuprofen as PDA therapy and the remaining 45 out of 51 neonates received paracetamol therapy to treat PDA. Ibuprofen used for DAP therapy can be oral or i.v.[17]. Ibuprofen in i.v. is not available in some countries.[18] The majority of samples used paracetamol. Paracetamol is used as a therapy for Persistent Ductus Arteriosus because it has been shown to reduce prostaglandin synthesis. However, the actual mechanism of action of Paracetamol in closing AD is still a controversy. Paracetamol has only very weak peripheral PG-related effects and exerts its main effect via the central nervous system.[19] Some researchers suggested that paracetamol was very beneficial over ibuprofen because paracetamol does not cause peripheral vasoconstriction. Thus, it can be used in neonates with ibuprofen contraindicated.[20] Paracetamol does not have has the effect of gastric irritation and inflammation like other classes of NSAIDs. Therefore, it leads paracetamol to be one of the best therapeutic options for PDA cases.

Low doses of paracetamol have proven to be harmless. It does not cause side effects and it is effective in closing PDA.[21] However, when used in large doses, paracetamol can cause severe liver necrosis to impaired liver function.[22] In the research, there were no patients who had hepatotoxicity. Ibuprofen can shift the binding of bilirubin with albumin, causing hyperbolicubinemia in neonates. This occurs because newborns have low plasma protein concentrations and albumin-binding capacity. Thus, it affects their ability to bind to drugs that are extensively bound to plasma proteins. The low amount of plasma protein will cause several adverse drug effects, such as hyperbolarubinemia [16]. Paracetamol has a lower risk of hyperbilirubinemia than patients using ibuprofen.[10] The results of this research indicated that there were 18 neonates suffering from hyperbilirubinemia, but there were no lab results stating that hyperbilirubinemia in cases of neonatal PDA was caused by pharmacological therapy. Hyperbilirubinemia is common in newborns.

In this research, it was found that ibuprofen succeeded in closing Ductus Arteriusus by 4/6 neonates (66.67%) and paracetamol was able to close DA by 30/45 neonates DAP (66.67%). However, this result was lower than previous researches. Thus, the further data and research are needed to study this case.

B. The Success Factor of Pharmacological Therapy Based on Test Results

The test results using the correlation method in SPSS showed that birth weight with successful therapy in Persistent Ductus Arteriosus neonates in dr. Soetomo did not show a significant relation. This could be due to the uneven distribution of the sample in each category, there were 18 neonates with DAP (35.3%) who were born in the low birth weight category (<2500 grams), 31 neonates (60.78%) were born with body weight adequate birth weight (2500 - 4000 grams), and 2 (3.92%) DAP neonates were born overweight (> 4000 grams). The sample gap occurred because neonates who were born underweight would undergo further surgery to treat PDA. Hence, they would be included in the exclusion category in this research.

The test results using the correlation method in SPSS showed that the gestation period with the success of therapy had a significant relation. The gestation period determines the quality of the newborn's health because it was related to the readiness of the structure and function of organs for extrauterine life. The lower the gestation period was the higher the risk of the neonates developing PDA because of the worsening cardiopulmonary immaturity. The gestation period would affect the formation of cells in the smooth muscle media tunica of intrauterine organs and the response to oxygen at birth. Preterm neonates tended to have a low response to oxygen but had a high sensitivity to the effects of vasodilation and prostaglandin E2 and nitric oxide.[22] This was different from term or posterm neonates born, in the third trimester of pregnancy. The Ductus Arteriosus muscle would become thicker and experience sensitivity to systemic prostaglandins produced by the placenta and Ductus Arteriosus itself.[23] Neonates with a low gestation period will also have a low Ductus Arteriosus closure rate.[22] Preterm neonates with PDA tend to suffer from various complications that aggravate the condition, such as RDS (respiratory distress syndrome), pulmonary bleeding, bronchopulmonary dysplasia, necrotizing enterocolitis (NEC), kidney failure, intraventricular hemorrhage (IVH), periventricular leukomalacia (PLV), cerebral palsy, until falling in a condition that requires further ventilation and even death.[25] The lower the gestation period, the lower the maturation

of the liver and kidneys. When the liver has not yet fully formed, this needs to be watched out when using paracetamol as a pharmacological therapy because more paracetamol is metabolized in the liver. Hence, the less gestational age will worsen the ability of drug absorption, distribution, metabolism and excretion.

The test results using the correlation method in SPSS showed that the defect size and the success of therapy had a significant relation. The larger the defect size, the smaller the success of pharmacological therapy. In normal and healthy neonates, the left side of the heart will pump clean blood (containing O_2) to the whole body and the right side of the heart will pump dirty blood (full of CO_2) to be channeled to the lungs. However, in neonates with PDA, there will be blood pumped from the aorta to the lungs or vice versa due to an open lumen. The direction of back flow (shunt) depends on the difference in resistance and pulmonary circulation with systemic circulation.[23] In large PDA, the neonate would breathe faster and louder than usual. The lungs of a neonate with large DAP would have a higher pressure because more blood is pumping in the lungs. The increase in the amount of blood in the pulmonary circulation will cause an increase in pulmonary fluid volume, decrease pulmonary compliance, difficulty breathing, and cause edema in neonates. Meanwhile, the increased blood flow in the left ventricle will cause the ventricle to overload, the ventricle will experience dilation and hypertrophy which in turn will cause a decrease in left ventricular function which can lead to heart failure.[24] While a small PDA size tends to cause mild to moderate symptoms due to heart and lungs don't have to work hard. In some cases, the clinical symptoms that appear are the finding of a characteristic murmur. The size of PDA greatly affects the clinical manifestations experienced by patients [25.] Thus, it can be concluded that the larger the size of the defect will cause more severe clinical symptoms and ultimately worsen the outcome of therapy.

Conclusion

In this research, Persistent ductus arteriosus is found more in male neonates, normal birth weight, and gestational period, moderate defect size before pharmacological therapy, pharmacological treatment options using paracetamol, comorbid diseases Atrial Septal Defect in the category of cardiac comorbidities and hyperbilirubinemia in the category of non-cardiac comorbidities. The success factors of administrating ibuprofen and paracetamol to neonates with persistent ductus arteriosus from January 1, 2016 to March 3, 2020 are affected by the gestation period and the size of the ductus arteriosus defect before being given pharmacological therapy.

Ethical Clearance: This study protocol had been approved by the Faculty of Medicine, Airlangga University, Surabaya, East Java, Indonesia.

Conflict of Interest: The authors declare that they have no conflict of interest.

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