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Research Article

The Relationship between the Therapy Cycle and the Success of Patent Ductus Arteriosus Closure Treatment in Premature Babies

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ABSTRACT

Patent Ductus Arteriosus (PDA) is a disease often found in premature babies characterized by failure or delay in the closure of the Ductus Arteriosus (DA). PDA frequently occurs in babies born prematurely and is caused by high levels of prostaglandin E2 (PGE2) due to incomplete closure of the ductus and lung function. This condition can disrupt hemodynamics, so it needs to be closed. Closure can be done using cyclooxygenase (COX) inhibitor drugs, such as Indomethacin and Ibuprofen. Apart from that, paracetamol can also be used as an alternative to trigger the closure of the PDA. This study aims to establish the correlation between the medical intervention cycle and the efficacy of closing Patent Ductus Arteriosus (PDA) in preterm infants. The investigation employed an observational, retrospective, analytical approach along with a cross-sectional layout. The sampling technique in this research was total sampling. The sample obtained was 24 newborns, which was secondary data in the form of medical records obtained at the medical records installation of RSUP Haji Adam Malik Medan and Mother and Child Stella Maris Hospital Medan. All data were then processed and analyzed, and statistical tests were carried out using Spearman correlation tests with the SPSS application. The outcomes of this investigation, utilizing the Spearman correlation analysis, revealed a significant value of $p = 0.001$ ($p<0.05$) concerning the association between the duration of treatment and treatment efficacy and a significant value of $p = <0.001$ ($p<0.05$) concerning the treatment cycle and treatment efficacy. Thus, there was no relationship between the treatment cycle and the success of the treatment.

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INTRODUCTION

Patent Ductus Arteriosus (PDA) is the failure of a ductus arteriosus to close after birth. A normal ductus arteriosus will close within two to three days after the baby's birth (Amelia, 2019). Patent Ductus Arteriosus often occurs in infants born prematurely due to high levels of prostaglandin E2 (PGE2), due to incomplete ductal formation, abnormal lung function, and decreased sensitivity of the ductal muscles to changes in oxygen and calcium partial pressure. If PDA is left without therapeutic intervention, it can cause other complications to appear and can even lead to death (Djatmiko, 2017). Almost all congenital anomalies are recently accompanied by PDA, which accounts for 6% to 11%. In every 2,500 to 5,000 live births that occur, one baby may be found with PDA. In Indonesia, 4,000 infants with PDA are born each year. Preterm infants have a higher incidence of PDA, with 8 of every 1,000 births of full-term infants (Amelia, 2019). Recently, there has been an increase in the incidence of PDA, with 1 in 500 full-term newborns. PDA has occurred in more than 50% of preterm neonates, and its presence is associated with high morbidity and mortality rates (Amelia et al., 2021). For infants with a gestational age of 30-37 weeks, 10% of them experience failure of ductus arteriosus (DA) closure by the fourth day, while for infants with a gestational age of 25-28 weeks and 24 weeks, the numbers reach 80% and 90%, respectively (Aritonang et al., 2021).

The clinical manifestations of Patent Ductus Arteriosus (PDA) typically correlate with the pulmonary blood flow volume. The magnitude of the shunt is contingent upon factors like the dimensions of the PDA (including length, tortuosity, and diameter) and the resistance within the pulmonary vasculature (Marcdante et al., 2014). While insignificant PDAs often remain asymptomatic, moderate to substantial PDAs can manifest diverse symptoms like cardiac insufficiency coupled with a reduction in pulmonary vascular resistance. Hemodynamic PDA stands out as a prevalent subtype among instances of PDA, with hemodynamically significant cases potentially heightening the susceptibility to various complications such as bronchopulmonary dysplasia, intraventricular hemorrhage, and necrotizing enterocolitis (Aritonang et al., 2021).

The therapeutic interventions commonly employed involve either pharmaceutical agents or surgical procedures. Nevertheless, owing to its minimally invasive nature and its capacity to forestall numerous concomitant conditions linked to surgery, such as vocal cord palsy, pulmonary dysplasia, and neurosensory impairments, pharmaceutical treatment is frequently advocated as the primary therapeutic approach (Zhang et al., 2023). The established pharmacological regimen for these scenarios entails using Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) like indomethacin and ibuprofen, which impede prostaglandin synthesis by inhibiting cyclooxygenase activity (Aritonang et al., 2021). The efficacy of indomethacin tends to be restricted in full-term neonates, diminishes with advancing postnatal age, and is confined to the initial 3 to 4 weeks of life. Additionally, clinical data suggest that indomethacin and ibuprofen exhibit comparable efficacy in managing PDA among full-term infants (Amelia, 2019). Administering ibuprofen at a standard dosage regimen has achieved successful "ductal closure" in approximately 70-80% of neonatal PDA cases (North West Neonatal Operational Delivery Network, 2020). Despite the equivalent effectiveness of ibuprofen and indomethacin in eliciting ductal closure, ibuprofen is favored due to its lower incidence of adverse

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effects (Aritonang et al., 2021). In addition to ibuprofen and indomethacin, paracetamol may be utilized as part of the pharmacotherapeutic armamentarium in such instances (Bardanzellu et al., 2017). Nonetheless, the effectiveness of paracetamol in effecting ductal closure is approximately 15% (North West Neonatal Operational Delivery Network, 2020). Based on the description, research on medical treatment has shown the ability to trigger PDA closure. Hence, the researcher wants to know the efficacy of medical therapy in closing PDA in preterm infants based on several variables assessed.

METHODS

Study design and patients

The utilized research design was descriptive-analytic, employing a cross-sectional methodology to establish the correlation between the treatment cycle and the efficacy of closing Patent Ductus Arteriosus in neonates at Haji Adam Malik General Hospital and RSIA Stella Maris from 2021 to 2023. All patients' medical records with Patent Ductus Arteriosus closure were scrutinized for clinical data, fundamental demographic information, anthropometric measurements, and echocardiography results. Patent Ductus Arteriosus (PDA) denotes the inability of a ductus arteriosus to seal postnatally. In contrast, a typical ductus arteriosus should naturally occlude within two to three days following the infant's delivery.

Sampling Method

Sampling was carried out using the total sampling method. The research sample was all premature babies diagnosed with Patent Ductus Arteriosus (PDA) with inclusion criteria in the form of gender, weight, PDA size, treatment cycle, and treatment success with complete medical records at Haji Adam Malik General Hospital and Stella Maris Hospital from January 2021 - June 2023 with the number of research samples being the entire population that met the inclusion and exclusion criteria.

Data Collection

The baseline characteristics of the patients were using secondary data in the form of medical record data obtained from Haji Adam Malik General Hospital and Stella Maris Hospital, Medan City. This research has been ethically approved by the ethical committee.

Statistical analysis

The data was analyzed using a correlation test. To determine the relationship between the treatment cycle, length of treatment, and treatment success, a statistical product and service solution (SPSS) that analyzes the independent and dependent variables together was used.

RESULTS

Demographic and clinical characteristics

Data was obtained based on medical records of patients suffering from Patent Ductus Arteriosus (PDA) from 2021 to 2023 who met the inclusion criteria, totaling 24 people. The demographic and clinical characteristics of the patient are outlined in Table 1. Based on the table below, PDA is more common in premature female infants (58.3%). Low birth weight infants are the largest birth weight sample group (41.7%). Patients with moderate PDA types were the most commonly diagnosed condition in the sample group (41.7%). Preterm infant patients with PDA more often get help with the treatment cycle once (70.8%) (Table 1). All of the birth weight group of premature infants with PDA more often get treatment with a once cycle compared to a twice cycle (Table 2).

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Table 1. Demographic and clinical characteristics of patients with Patent Ductus Arteriosus (PDA) included in the study (n=24)

Patients' Characteristics	Frequency (%)
Gender	
Male	10 (41.7)
Female	14 (58.3)
Birth Weight	
Extremely Low Birth Weight (1000 - 1499 gram)	6 (25)
Very Low Birth Weight (1500 - 1999 gram)	6 (25)
Low Birth Weight (2000 - 2499 gram)	10 (41.7)
Normal Birth Weight (2500 - 3000 gram)	2 (8.3)
Types of PDA	
Small (1-1,5 mm)	9 (37.5)
Moderate (1,5-3 mm)	10 (41.7)
Large (>3 mm)	5 (20.8)
Treatment Cycle	
Once	17 (70.8)
Twice	7 (29.2)

Table 2. Distribution of Birth Weight by Treatment Cycle in Premature Infants with Patent Ductus Arteriosus (PDA)

Birth Weight	Treatment Cycle Frequency (%)	
	Once	Twice
Extremely Low Birth Weight (1000 - 1499 gram)	4 (66.7)	2 (33.3)
Very Low Birth Weight (1500 - 1999 gram)		
Low Birth Weight (2000 - 2499 gram)	5 (83.3)	1 (16.7)
Normal Birth Weight (2500 - 3000 gram)	7 (70)	3 (30)
	1 (50)	1 (50)

Treatment Success in Premature Infants with PDA

The results of this study showed that the most extensive sample group was premature infant patients with PDA who had successfully been treated and had a shrinking PDA size of 10 people (41.7%). The sample group of premature infant patients with PDA who had successfully treated and had a persistent and closing PDA size had the same number of 7 people (29.2%) (Table 3).

Results Analysis

The data collected were analyzed using the correlation test. The relationship between the treatment cycle and treatment success was carried out with the help of a computerized statistical program that analyzed the independent and dependent variables together. The correlation test on the two variables of this study can be stated in the following table:

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Table 3. Distribution of Treatment Success in Premature Infants with PDA

Treatment Success	Frequency (%)
Persistent	7 (29.2)
Shrinking	10 (41.7)
Closing	7 (29.9)

Table 4. Relationship between Treatment Success and Treatment Cycle

Treatment Success	r	P
Treatment Success - Treatment Cycle	0.240	0.259

The normality test found that the data in this study were not normally distributed. The Spearman statistical test identified the relationship between the treatment cycle and treatment success in this study. Table 4. Shows the value of p = 0.259 (p>0.05) in the relationship between treatment success and treatment cycle. This result indicates no significant relationship between the two variables, indicating an association between the treatment cycle and success.

DISCUSSION

Based on the results of the study, it was found that the highest number of preterm infant patients suffering from PDA were women, with 14 (58.3%) out of 24 cases, slightly more than men with 10 (41.7%). This is comparable to research conducted by Borges-Lujan et al. (Borges-Lujan et al., 2017). The study was also conducted at RSUD by Dr. Soetomo Surabaya, conducted by Utomo et al., which stated that the gender composition was more female than male patients (Utomo et al., 2022). However, these studies showed that gender did not significantly correlate with PDA treatment (Liu et al., 2021). The variation in the incidence of PDA among preterm infants based on gender was observed, revealing a higher prevalence among female preterm infants compared to their male counterparts. This discrepancy can be attributed to the quicker onset of the initial phase of functional closure of the ductus arteriosus in male infants, in contrast to female infants. Additionally, it was noted that during the onset of the constriction of the ductus arteriosus, a combined effect of oxygen-mediated contraction and withdrawal of prostaglandin E2-induced relaxation plays a synergistic role (Borges-Lujan et al., 2017).

From the results of this study, it was found that the most premature babies with PDA were babies with a birth weight of 2000-2499 grams with a total of 10 people (41.7%) out of 24 cases, while the least number of sample groups were premature babies with PDA with a birth weight range of 2500-3000 grams as many as two people (8.3%). This contradicts the research conducted at RSUD Dr. Soetomo Surabaya, conducted by Utomo et al, which states that the highest number of infant patients with PDA have a weight range of <1500 grams (Utomo et al., 2022). This is also different from research conducted by Terrin et al. This is because the weight of premature babies influences the behavior and physiology of premature babies (Terrin et al., 2021). The smaller the body weight of premature babies, the more complex

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problems arise with the baby's body functions (Kuraesin et al., 2021).

Based on the study's results, it was found that the most significant number of sample groups of preterm infant patients with PDA were patients with moderate PDA types, totaling 10 (41.7%) out of 24 cases. In comparison, the fewest were preterm infant patients with large PDA types, totaling five people (20.8%). The results of this study follow the results of research by Sari et al., where the most significant number of PDA infant patients are patients with moderate PDA types but also contradict research by Sari et al., where it was found that the least number of PDA patients were patients with small PDA types (Sari et al., 2016). In addition, the results of this study also contradict research conducted by Chinawa et al., which found that the highest number of infant PDA patients were patients with large PDA types and the fewest were patients with small PDA types (Gillam-Krakauer, 2023). The disparate outcomes of each investigation may stem from the reduced significance of PDA echocardiography findings within the initial seventy-two hours of life, attributed to the immediate transitional period during PDA closure (Chinawa et al., 2021). The extent of the transductal shunt is not solely determined by the transductal diameter. Still, it is also impacted by pulmonary and systemic vascular resistance, as well as the compensatory capacity of undeveloped myocardium contingent upon the timing of birth (Rios et al., 2018). These various elements contribute to the diminished reliability of echocardiographic assessments of PDA. (Choi et al., 2021)

The results of this study also show that preterm infants with PDA more often get help with the treatment cycle once, with a total of 17 people (70.8%), while preterm infants with PDA who get help with the treatment cycle twice are fewer than seven people (29.2%). In addition, when viewed based on birth weight, it can be seen that each birth weight group also more often gets help with the treatment cycle once or twice. This is comparable to research by Terrin et al. It was found that the number of patients who only needed one treatment cycle was more than those who needed more than one treatment cycle (Terrin et al., 2020).

This study also found that the most extensive sample group was premature infant patients with PDA who had successful treatment, with the results of a shrinking PDA size of 10 people (41.7%). The sample group of premature infant patients with PDA who had successful treatment with the results of a closing PDA size of 7 people (29.2%) and the sample group of premature infant patients with PDA who had successful treatment results without changes in the size of the PDA that became settled had the same number of 7 people (29.2%). This shows that there are more successful treatments that change the size of the PDA. Successful treatment is said to occur if the PDA size has a diameter of <2.00mm, following research by Su et al. This is comparable to research by Sari et al., where the number of patients who were found to have successful treatment was more than the number of patients who had unsuccessful treatment (Su et al., 2020; Sari et al., 2016).

In a study by Olgun et al., it was mentioned that repetition of treatment cycles would increase the success rate of treatment, where the success rate of the second cycle of medical treatment of PDA is higher than the first cycle (Olgun et al., 2017). Furthermore, repeated cycles of medical therapy appear to be effective and safe in PDA closure. However, the number of patients in the second cycle of medical therapy is fewer than in the first cycle of therapy, as the second cycle is only performed if the first cycle fails. In addition, the first cycle has also had a high success rate. Thus, there were more treatment

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successes than failures, and the number of occurrences of the second cycle was less than in the first cycle.

In this study, researchers did not find an association between the treatment cycle and treatment success. The statistical test results of the relationship between treatment cycle and treatment success showed p = 0.259 (p>0.05). The results of this relationship indicate no significant relationship between the treatment cycle and treatment success. This is also comparable to research conducted by Terrin et al., where closure in the first cycle had an insignificant relationship with a p-value = 0.596 and in the second cycle had a relationship with PDA closure with a p-value = 0.143 (Terrin et al., 2020).

This can be caused by the study's limitations in looking for the relationship between the treatment cycle and treatment success because several things, such as the small number of samples, can cause it. The number of samples is due to researchers only looking for relationships in samples of premature babies, which is only 15% of the 1000 births in the world, and as much as 9-30% in Indonesia, according to research by Kuraesin et al. This is comparable to research by Ningsih & Indrasari, which found that the number of preterm babies is less than that of normal birth babies (Kuraesin et al., 2021; Ningsih & Indrasari, 2021).

This study also has other limitations, namely that it uses a retrospective study that examines data from pre-existing medical records. According to Hess and Faarc, retrospective study research is cheaper and more accessible. It can help issue hypotheses, but it has disadvantages, such as requiring accuracy from writing medical records, so that there are difficulties in finding essential data that are not recorded (Hess, 2014). Meanwhile, the use of prospective studies, according to Song and Chung, has the advantage of monitoring the progress of disease incidence from beginning to end to obtain complete data and varied results. However, this study requires high costs, an extended research duration time to record complete follow-up of the sequence of disease events, and the difficulty of maintaining follow-up of diseases that can be lost. Therefore, the researcher used a retrospective study (Song & Chung, 2010).

CONCLUSION

Based on the results of data analysis and discussion of this study derived from the medical records of premature infants with PDA at Haji Adam Malik Hospital and RSIA Stella Maris, it can be concluded that this study did not show a significant relationship between the treatment cycle and treatment success.

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