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DIFFERENCES OF BIRTH WEIGHT AND ONSET OF ACHOLIC STOOL BETWEEN EXTRAHEPATIC AND INTRAHEPATIC CHOLESTASIS

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Abstract

Background*: Biliary atresia (extrahepatic cholestasis) and neonatal hepatitis (intrahepatic cholestasis) are the two main causes of cholestasis. It is important to distinguish the type of cholestasis to determine management. Patients with intrahepatic cholestasis have birth weight lower than extrahepatic cholestasis. The onset of acholic stool in extrahepatic cholestasis usually appears in 15-30 days of first life. The study aims to identify differences in birth weight and onset of acholic stool between the types of cholestasis.* ***Method:*** *A retrospective study on cholestasis children aged under 2 years was conducted at Dr. Soetomo General Academic Hospital, Surabaya from January 2012 to December 2016. A thorough history of birth weight and onset of acholic stool were undertaken. Based on histopathology liver biopsy patients were classified into two groups: I (extrahepatic cholestasis) and II (intrahepatic cholestasis). Data was analyzed using Mann Whitney U with p<0.05 being significant.* ***Result:*** *A total of 84 children were included, 55% were male. 40 children suffered from extrahepatic cholestasis (mean age 4.8 ± 2.6 months old) and 44 children suffered from intrahepatic cholestasis (mean age 2.9 ± SD 3.8 months old). The mean birth weight between extrahepatic and intrahepatic cholestasis was 2813 ± 704 gram vs 2717 ± 577 gram) (p=0.29). The mean onset of acholic stool between extrahepatic and intrahepatic cholestasis was 43.0 ± 60.6 days vs 26.6 ± 39.7 days (p=0.27).* ***Conclusion:*** *There is no difference in birth weight and onset of acholic stool between extrahepatic and intrahepatic cholestasis.*

Keywords: *Acholic stool, Birth weight, Children, Extrahepatic Cholestasis, Intrahepatic cholestasis,*

INTRODUCTION

Cholestasis is a condition of decreased bile production and/or excretion. Conjugated hyperbilirubinemia, which is present at birth or develops within the first few months of life, is often referred to as neonatal cholestasis. Conjugated hyperbilirubinemia is an elevation of conjugated bilirubin >20% of total serum bilirubin and >1 mg/dL (Pandita et al., 2018). Cholestatic jaundice is a rare condition that indicates hepatobiliary dysfunction. Cholestatic jaundice occurs in 1 out of every 2,500 infants and is therefore often missed for diagnosis (Feldman and Sokol, 2013).

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The most common causes of cholestatic jaundice in the first months of life are biliary atresia and neonatal hepatitis, representing the majority of cases. For optimal treatment and prognosis, early recognition by the primary care physician and timely referral to a pediatric gastroenterologist or hepatologist is essential (Fawaz et al., 2017).

Birth weight and onset of acholic stool are two clinical manifestations that are usually used to differentiate extrahepatic cholestasis from intrahepatic cholestasis (Lee and Chai, 2010). Patients with intrahepatic cholestasis have birth weight lower than extrahepatic cholestasis. The onset of acholic stool in extrahepatic cholestasis usually appears in 15-30 days of first life (Bellomo-Brandao et al., 2010). There is a rare study about birth weight and onset of acholic stool between the types of cholestasis therefore, this study aims to identify differences in birth weight and onset of acholic stool between extrahepatic cholestasis and intrahepatic cholestasis.

METHOD

A retrospective study on cholestasis children was conducted at Dr. Soetomo General Academic Hospital, Surabaya from January 2012 to December 2016. All cholestasis children aged under 2 years old who had done a liver biopsy. The site of this study was the pediatric ward, Dr. Soetomo General Academic Hospital, Surabaya, East Java. Patient data were obtained from medical records. Histopatology examination of liver biopsy was performed by an anatomy pathologist. Children aged under 2 years diagnosed with cholestasis who had run liver biopsy were involved. Based on the result of histopathology liver biopsy, patients were classified into two groups: I (extrahepatic cholestasis) and II (intrahepatic cholestasis). A thorough history of birth weight and onset of acholic stool were undertaken. Statistical analysis of Mann Whitney U was used with $p<0.05$ being significant. Analysis was performed using SPSS software. The study was approved by the Ethics committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (No 117/Panke.KKE/II/2017).

RESULT AND DISCUSSION

A total of 84 children were studied, forty-six (55%) children were male with a mean age were 4.8 ± SD 2.6 months old on extrahepatic cholestasis and 2.9 ± 3.8 months old on intrahepatic cholestasis. From the histopathology of liver biopsy, 40 (48%) showed extrahepatic cholestasis and 44 (52%) were intrahepatic cholestasis. (Table 1).

Table 1. Baseline characteristics

Characteristic	n (%)
Sex	
Male	46 (55)
Female	38 (45)
Histopatology liver biopsy	
Extrahepatic	40 (48)
Intrahepatic	44 (52)
	Mean ± SD
Age (month)	
Extrahepatic	4.8 ± 2.6
Intrahepatic	2.9 ± 3.8
Birth weight (gram)	
Extrahepatic	2813 ± 704
Intrahepatic	2717 ± 577
Onset of acholic stool (day)	
Extrahepatic	43.0 ± 60.6
Intrahepatic	26.6 ± 39.7

The mean birth weight between extrahepatic and intrahepatic cholestasis was 2813 (SD 704) grams vs 2717 (SD 577) grams (p=0.29). The mean onset of acholic stool between extrahepatic and intrahepatic cholestasis was 43.0 (SD 60.6) days vs 26.6 (SD 39.7) days (p=0.27) (Figures 1 and 2).

Figure 1. Mean birth weight between extrahepatic and intrahepatic cholestasis

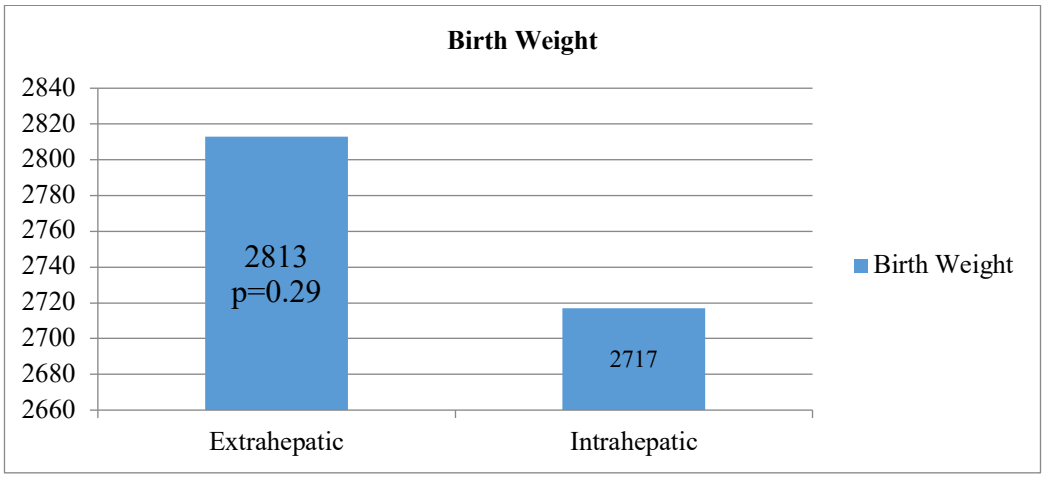

Figure 1 shows that the mean of birth weight patients with extrahepatic cholestasis was 2813 grams and the birth weight of patients with intrahepatic cholestasis was 2717 grams. The birth weight of patients with extrahepatic cholestatic was a little bit bigger than patients with intrahepatic cholestasis. The result of data analysis using the Mann-Whitney U test obtained p value 0.29. There was no difference in birth weight between patients with extrahepatic and intrahepatic cholestasis (p>0.05).

Figure 2. Onset of acholic stool between extrahepatic and intrahepatic Cholestasis

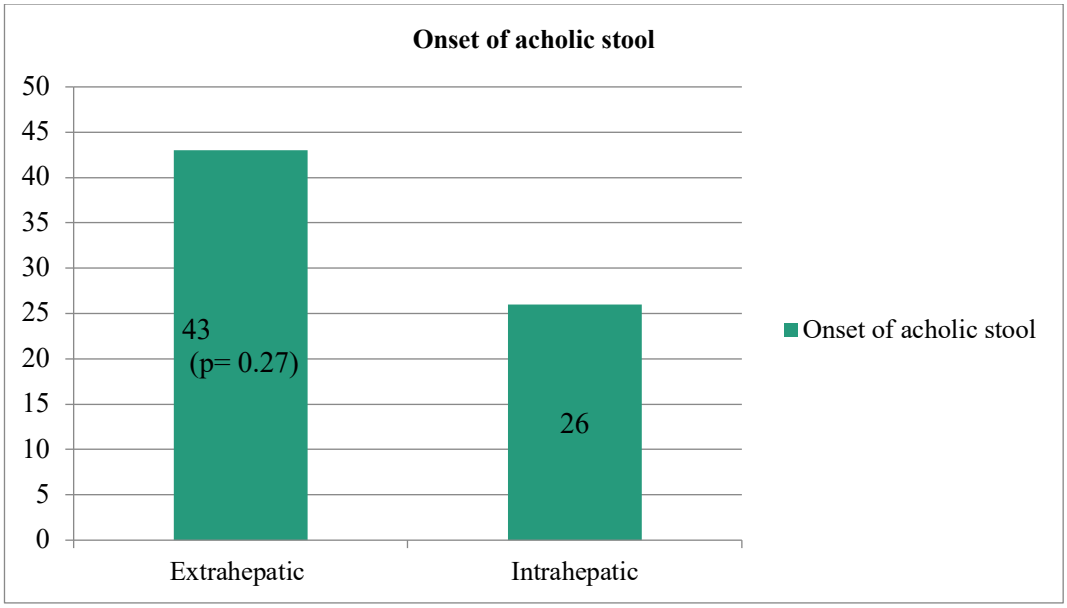

Figure 2 shows that the mean onset of acholic stool in patients with extrahepatic cholestasis was 43 days and patients with intrahepatic cholestasis were 26 days. The result of data analysis using the Whitney U test obtained a p-value of 0.27 ($p<0.05$). So statistically that was no difference in the onset of acholic between patients with extrahepatic and intrahepatic cholestasis.

Cholestatic jaundice in the first three months of life is a condition that occurs due to a reduction in the flow and/or excretion of bile and can be caused by a variety of conditions. Neonatal cholestasis should be considered in all infants with prolonged jaundice or jaundice at more than 2 weeks of age, or earlier in the presence of other clinical signs such as hepatomegaly, failure to thrive, yellow stools, or dark urine. Although rare, neonatal cholestasis can be a life-threatening cause of liver damage. However, delay in diagnosis of neonatal cholestatic disorders, especially biliary atresia, is still a health problem today. Misdiagnosis as physiologic jaundice, lack of national screening for genetic disorders, and presence of pigmented stools are common causes. of delayed diagnosis (Pandita et al., 2018).

Biliary atresia (extrahepatic cholestasis) and neonatal hepatitis (intrahepatic cholestasis) are the two main causes of cholestasis. It is important to distinguish the type of cholestasis to determine a medical management and surgical intervention as soon as possible (Pandita et al., 2018). Improvement in bile flow may occur if a hepato-portoenterostomy is performed before 2 months of age. If inadequately treated, biliary atresia patients may progress to end-stage liver disease and eventually require liver transplantation (Kobayashi et al., 2020).

Differentiating the type of cholestasis in our study based on the histopathology liver biopsy. Liver biopsy is an invasive test used in addition to other clinical methods to determine the etiology of cholestasis in the neonate. In one study, biopsies were found to contribute new findings to the diagnostic workup in 36.2 percent of cases, with an associated overall complication rate of 6.9 percent (Chaudhry et al., 2019). Liver biopsy performs well with a sensitivity of 95.1% and specificity of 91.6% in the diagnosis of extrahepatic cholestasis leading to biliary atresia (Ali et al., 2024). Extrahepatic biliary atresia associated with other diseases can generally be differentiated by the histopathologic examination and can help to

determine the need for surgical exploration in 90 to 95 percent of the patients. (Fawaz et al., 2017).

Liver histopathology is necessary to confirm the presence of intrahepatic cholestasis and extrahepatic cholestasis. Some of the liver histopathologic features obtained to differentiate between intra- and extrahepatic cholestasis include periportal duct proliferation, portal duct proliferation, portal expansion, cholestasis in the neoductus, foci of myeloid metaplasia, and portal-portal bridges. The finding of foci of myeloid metaplasia suggests intrahepatic cholestasis. Meanwhile, in extrahepatic cholestasis, periportal duct proliferation, portal duct proliferation, portal expansion, cholestasis in neo-ducts, portal cholestasis, and portal-portal bridges can be found (Ahmed et al., 2021).

Birth weight was one of the clinical parameters that can distinguish extrahepatic cholestasis from intrahepatic cholestasis. In our study, the mean birth weight in extrahepatic cholestasis more higher than in intrahepatic cholestasis, and the difference was not statistically significant. The study in Pakistan mentioned that the mean age was recorded as 118.01 days + 118.1 SD (Bilal et al., 2022). Another study showed that the mean age of cholestasis was 63.94 ± 20.62 days (Ali et al., 2024). A study from Bellomo-Brandao shows a different result which is there were significant differences in birth weight between extrahepatic and intrahepatic cholestasis (Bellomo-Brandao et al., 2010). A study at Dr. Soetomo General Academic Hospital, Surabaya stated that full-term and normal weight newborns have a higher risk of developing biliary atresia than those with low birth weight or premature birth (Yana et al., 2023).

The typical findings in an infant who has cholestasis are protracted jaundice, scleral icterus, acholic stools, dark yellow urine, and hepatomegaly. The report of pale stools by the parent or observation of clay-colored stool by the physician raises the suspicion of cholestasis (De Bruyne et al., 2011). Acholic stools in an infant should always prompt further evaluation. patients who have biliary atresia are critical (Feldman and Sokol, 2013). Biliary atresia had significantly more frequent acholic stool than neonatal hepatitis (Gürlek Gökçebay et al., 2015). Three clinical features considered sensitive to differentiate extrahepatic cholestasis in biliary atresia from neonatal hepatitis are the presence of acholic or variable stools on

admission, a firm/hard liver consistency, and a palpable liver ≥4 cm (sensitivity 77%, 80%, and 94%, respectively), but the specificity is low (51%, 65%, and 39%) (Lee and Chai, 2010).

In our study, the mean onset of acholic stool between extrahepatic was longer than intrahepatic cholestasis, but it was not significant. Although the presence of acholic stool had a 100% specificity for biliary atresia, its sensitivity was low at 58%. However, it was the first readily significant clinical presentation that could lead to extensive diagnostic evaluation on biliary atresia.

Delay in diagnosis of biliary atresia beyond 60–100 days of age may reduce the longevity of the native liver and increase morbidity in infants with biliary atresia, although the ideal surgical timing remains controversial (Jancelewicz et al., 2015). In our study birth weight and onset of acholic stool between extrahepatic and intrahepatic have no significant difference, the physician should be considered biliary atresia even though the birth weight was low or the onset of acholic stool was late.

CONCLUSION AND SUGGESTION

There is no difference in birth weight and onset of acholic stool between extrahepatic and intrahepatic. Further cohort studies with larger sample sizes was needed to evaluate any clinical manifestation to differentiate the type of cholestasis.

DECLARATION

Conflict of Interest

Author declare there is no conflict of interest in this research

Authors' Contribution

All author contribute from concept until writing draft article.

Ethical Approval

Research Ethics Committee **of** Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (No 117/Panke.KKE/II/2017).

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Data Availability

The data supporting this research are available from the authors on reasonable request.

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