Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 8, No. 6, 5075-5081
2024
Publisher: Learning Gate
DOI: 10.55214/25768484.v8i6.3113

The applications of Ursodeoxycholic acid in infant with cholestasis: A retrospective cohort analysis

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Abstract: Biliary atresia is the predominant etiology of cholestasis in early infancy. Impairment of bile fluid excretion results in elevated bilirubin levels, causing a yellowing of the skin. Ursodeoxycholic acid is well-established to enhance liver function when taken promptly. The application of ursodeoxycholic acid for treating cholestasis in pediatric patients remains contentious. The objective of this study is to assess the impact of ursodeoxycholic acid treatment on liver biomarkers in infant with cholestasis. This was retrospective cohort study in infant with cholestasis who underwent ursodeoxycholic acid treatment for two weeks. Secondary data including aspartate aminotransferase, alanine aminotransferase, total bilirubin, and direct bilirubin were extracted from the medical records of the outpatient clinic in the Department of Child Health at Dr. Soetomo General Hospital, Indonesia (January 2020 - December 2023). The data was devided into two groups based on biopsy and examined utilizing SPSS version 23. This study included 64 participants. Statistics show an equal gender ratio. Ursodeoxycholic acid treatment in paediatric cholestasis patients can lower liver biomarker level. Levels of total bilirubin and direct bilirubin diminished in individuals both groups. Notable levels were recorded in individuals with normal biopsy outcomes (p=0.007 and p=0.012). Administration of ursodeoxycholic acid markedly elevated ALT levels in both the normal and abnormal liver biopsy outcome groups (p=0.031 and p=0.006). Ursodeoxycholic acid has been shown to be effective in improving liver function in infant with cholestasis. In order to avoid negative effects, the medication must be carefully administered to people who already have liver fibrosis.

Keywords: *Bilirubin, Infant, Pediatric cholestasis, Transaminase, Ursodeoxycholic acid,*

1. Introduction

Cholestasis is defined as a disturbance in the flow of bile fluid, characterized by an increase in direct/conjugated bilirubin levels (>1 mg/dL or > 17 mmol/dL) [1]. Unlike in adults, the majority of cholestasis in children is due to immaturity of the liver [2]. The incidence of severe neonatal jaundice in Southeast Asia ranged from 251.3 out of 100,000 live births, the second highest after Africa [3].

Management of pediatric cholestasis depends on the underlying etiology and stage of the disease. Treatment might be invasive or supportive [4]. Ursodeoxycholic acid is a hydrophilic bile acid that is designated as a first-line drug for primary biliary cholangitis by the Food and Drug Administration [5,6]. Cholestasis, apoptosis, inflammation, and free radicals such as reactive oxygen species (ROS) in cholestasis are inhibited by this bile acid through the mechanism of membrane and nuclear receptors activation [7,8]. In addition, ursodeoxycholic acid is also known as an immunomodulator related to the production of immunoglobulin, interleukin and tumor necrosis factor (TNF-α) [9]. Although this drug

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has been included in the national formulary, its use in children is still controversial (off label) [10–12]. Some countries still limit its use in infants [13].

In addition to providing MCT medium chain triglycerides (MCT) nutrition and fat-soluble vitamins and minerals, ursodeoxycholic acid is part of the standard regiment for cholestasis and acute hepatitis in infants at Dr. Soetomo Hospital [14]. A dose of 10-20 mg/kg/day divided into 2-3 doses could reduce bilirubin and AST level, while reducing pruritus symptoms due to cholestasis [15]. Although most hyperbilirubinemia is a physiological process, it is necessary to evaluate for liver dysfunction as early as possible if the onset is earlier (<24 hours) or more than 14 days to obtain optimal results [16].

Studies regarding the administration of ursodeoxycholic acid in infant is important to understand the benefits, risks, and mechanisms of the drug. Until now, there is still debate regarding the administration of ursodeoxycholic acid at a younger age. Therefore, this study was conducted to develop a strategy for the management of cholestasis therapy in infant.

2. Materials and Methods

This study employed an observational and analytical design, utilizing a retrospective cohort methodology. The data collected consisted of secondary data from pediatric cholestasis patients under one year old at Dr. Soetomo Hospital, Surabaya, Indonesia, during the period of 2020-2023. The subjects of this investigation were infants and children attending the Outpatient Clinic of the Department of Child Health at Dr. Soetomo Hospital in Surabaya, who underwent treatment with ursodeoxycholic acid from 2020 to 2023. The participants in this study consisted of individuals who fulfilled the specified inclusion and exclusion criteria. The study's inclusion criteria consisted of patients aged 1-12 months, diagnosed with cholestasis (direct/conjugated bilirubin >1mg/dL or >17mmol/L) prior to starting ursodeoxycholic acid treatment. Participants had to have received ursodeoxycholic acid at a dosage of 10 mg/kgBW/day, divided into three doses, for a minimum of 14 days. The drug was prescribed by the pharmacy installation of Dr. Soetomo Hospital. Additionally, there was a requirement for data on total bilirubin levels, direct bilirubin, AST, and ALT to be available both before and after the administration of ursodeoxycholic acid. Laboratory examinations were conducted at the Pathology Clinic Installation of Dr. Soetomo General Hospital. Analysis of liver biopsy performed at the clinical pathology department of Dr. Soetomo General Hospital. The criteria for exclusion in this study included patients with incomplete medical records, individuals whose ALT, AST, total and direct bilirubin data were collected at varying times, and those identified as extreme outliers.

The study employed a total sampling method utilizing a non-random sampling technique, encompassing all subjects who satisfied the inclusion and exclusion criteria. The sample was categorized into two study groups according to liver biopsy results: normal (group 1) and abnormal findings (group 2). Secondary data were obtained from medical record books and Electronic Medical Records (EMR). The collected data underwent examination, validation, coding, recapitulation, and tabulation, followed by appropriate statistical analysis. Descriptive analysis was employed to ascertain the characteristics of the study subjects, including age, gender, weight, height, total bilirubin levels, direct bilirubin, AST, and ALT. The Shapiro-Wilk test was employed to assess the normality of each study variable. A paired T-test was conducted when normal results were obtained ($p>0.05$). In cases where the results are abnormal ($p<0.05$), a difference test will be conducted using the Wilcoxon test. The difference in AST, ALT, total, and direct bilirubin values was calculated for each sample before and after the administration of ursodeoxycholic acid. Subsequently, comparison tests for the differences in mean levels of AST, ALT, total bilirubin, and direct bilirubin between groups were conducted using the unpaired T-test for normal distribution or the Mann-Whitney test for abnormal distribution. The analysis yielded significant results with $p<0.05$.

Before the study was conducted, the researcher submitted a research ethics from the Research Ethics Commission of Dr. Soetomo Hospital. The researcher had obtained approval, with a registration number: 1556/LOE/301.4.2/XII/2023.

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 8, No. 6: 5075-5081, 2024
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3. Results

This research involved a total of 65 infant. One patient was removed due to an outlier, notably an ALT level beyond 1000 U/L. A total of 64 youngsters were incorporated in the final analysis. The study participants were subsequently categorized into two groups based on the liver biopsy funding. Data distribution tests were performed using Shapiro-Wilk in both groups. Most of the parameters in this study had normal distribution. Continuous data are expressed as mean ± standard deviation for data that follow a normal distribution, or as median (minimum value-maximum value) for data that do not conform to a normal distribution. An unpaired comparison test was conducted between groups utilizing the Mann Whitney test, revealing that significant differences were observed solely in the parameters concerning the age of drug administration (Table 1).

Table 1.
Study subject characteristics.

Variable	Liver biopsy		p
	Group 1 (n=15)	Group 2 (n=49)	
Gender, n (%)			
Male	9 (28.1)	23 (71.9)	0.555
Female	6 (18.8)	26 (81.3)	
Age on drug administration (Months)	2 (1-5)	2 (1-9)	0.003*
Body weight (kg)	5 (±1.19)	4.9 (±0.97)	0.592
Body height (cm)	58.9 (±6.1)	59 (45-81)	0.656
Before treatment			
AST (U/L)	229.7 (±136.7)	231 (42-911)	0.330
ALT(U/L)	138 (38-450)	164 (30-641)	0.161
Total bilirubin (mg/dL)	7.7 (±3.34)	8 (±2.4)	0.716
Direct bilirubin (mg/dL)	10.7 (±4.9)	10.8 (±3.6)	0.968
After Treatment			
AST (U/L)	193.1 (±129)	221 (6-658)	0.296
ALT(U/L)	208 (66-932)	259 (6-925)	0.769
Total bilirubin (mg/dL)	4.9 (±3.8)	6.5 (±3.8)	0.157
Direct bilirubin (mg/dL)	6.7 (±5.4)	11.2 (±19)	0.187

Note: *significant result (p<0.05).

Table 2.
Level of biomarker before and after ursodeoxycholic acid drug administration.

Variable		Pre-UDCA	Post-UDCA	p
AST	Group 1	229.7 (±136.7)	193.1 (±129)	0.237
	Group 2	231 (42-911)	221 (6-658)	0.048*
ALT	Group 1	138 (38-450)	208 (66-932)	0.031*
	Group 2	164 (30-641)	259 (6-925)	0.006*
Total bilirubin	Group 1	7.7 (±3.34)	4.9 (±3.8)	0.007*
	Group 2	8 (±2.4)	6.5 (±3.8)	0.866
Direct bilirubin	Group 1	10.7 (±4.9)	6.7 (±5.4)	0.012*
	Group 2	10.8 (±3.6)	11.2 (±19)	0.006*

Note: *significant result (p<0.05).

The results of the examination of the four liver function biomarkers after administration of 10 mg/kgbb ursodeoxycholic acid for 2 weeks showed significant differences, except for the results of the AST in group 1 and total bilirubin in group 2 (Table 2). Most liver function indicators exhibited a decline in both cohorts. Ursodeoxycholic acid elevates ALT levels in individuals with and without prior liver fibrosis. A significant reduction in total and direct bilirubin levels was recorded in group 1, with

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 8, No. 6: 5075-5081, 2024
DOI: 10.55214/25768484.v8i6.3113

p=0.007 and p=0.012 (p<0.005). A significant reduction in direct bilirubin levels was seen in group 2 (p=0.006). The comparison analysis results indicated a substantial elevation in ALT levels in both group 1 and group 2 (p=0.031 and p=0.006).

4. Discussion

The findings of this study demonstrate that the majority of liver biomarker levels diminished following the injection of ursodeoxycholic acid in both age cohorts. Korean research in 2019 indicated that levels of ALT, AST, and gamma-glutamyl transferase (GGT) dropped by 40.3%, 33.9%, and 23%, respectively, following 4 weeks of ursodeoxycholic acid therapy [17]. A meta-analysis by Simental-Mendía demonstrated comparable findings, indicating that the treatment of ursodeoxycholic acid for almost one month significantly reduced AST levels (p <0.001) [18].

The alanine aminotransferase enzyme is more selective for hepatic injury and possesses a longer half-life of 45 to 47 hours, as it is mostly located in the cytoplasm of hepatocytes [19,20]. This study's results indicated that ALT levels in both groups elevated following the injection of ursodeoxycholic acid. The findings of this investigation contradicted earlier research. A meta-analysis done in China indicated that ursodeoxycholic acid decreased blood transaminase levels, namely ALT and AST, in children with cholestasis.[15] This elevation in serum levels actually did not indicate liver fibrosis, despite its prevalence in hepatic activity. The majority of individuals with liver cirrhosis had no elevation in ALT levels. A retrospective cohort study conducted in the United States revealed that 70 out of 78 cirrhosis patients (89.7%) exhibited ALT levels within the normal range [21].

Toxicity of ursodeoxycholic acid has been documented in several research. Following oral dosing, ursodeoxycholic acid is absorbed by the gut and enters the portal vein. In the portal triad, ursodeoxycholic acid is transported into hepatocytes in a taurine-bound form, with some entering the biliary channel. Tauro ursodeoxycholic acid (TUDCA) is oxidised to become lithocholic acid (LCA), which is hepatotoxic [22]. Lithocholic acid may induce non-specific damage to the bacterial cytoplasmic membrane owing to its lipophilicity and decontamination properties [23]. This situation may endure longer because to the relatively extended half-life of ursodeoxycholic acid, which ranges from 3.5 to 5.8 days [24]. Children with cholestasis have reduced liver maturity. As age progresses, liver function maturity and weight rise. This often happens at the age of two years [25,26].

Both total and direct bilirubin levels were shown to decrease after the administration of ursodeoxycholic acid to both of the groups. Group 1 had significantly different amounts of bilirubin than group 2, according to the findings of this investigation. When used as a choleretic agent, ursodeoxycholic acid has the potential to make bile fluid that contains 0.2% bilirubin more excreted. After conducting research at the Neonatal Intensive Care Unit (NICU) of Dr. Moewardi Hospital, it was found that the difference in total bilirubin levels between the treatment group and the control group was 3.18 ± 3.32. On the other hand, the difference between the two groups was 1.67 ± 4.50 (p <0.001) [22,27].

The results of this study indicate that ursodeoxycholic acid was able to reduce direct bilirubin levels in infant with cholestasis. Significant differences were found in the both groups. This was in line with the results of a previous systematic review studies showing that ursodeoxycholic acid administration in children with cholestasis might result in a significant decrease in direct bilirubin levels [18].

Cholestasis is marked by elevated direct bilirubin levels in the bloodstream. Previous studies done in China found elevated liver biomarker values, particularly direct bilirubin (p<0.01), in children with cholestasis compared to their healthy counterparts. In contrast to indirect bilirubin, direct bilirubin is water-soluble and hence does not need a protein transporter inside the bloodstream. The conjugated bilirubin proceeds to the colon to facilitate excretion (80%) as urobilinogen via faeces and urine, with a little portion being reabsorbed [28]. The toxicity of direct bilirubin is inferior to that of indirect bilirubin. Ursodeoxycholic acid lowers bilirubin levels by obstructing bilirubin reabsorption and enhancing bile flow and faecal elimination [29].

Ursodeoxycholic acid exhibits multiple mechanisms that protect hepatocytes. Farnesoid X receptor (FXR) is a nuclear receptor involved in this process [30]. This receptor targets 40 genes, the majority of which are involved in stimulating the bile signalling pathway. This nuclear receptor enhances bile

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ISSN: 2576-8484
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excretion from the liver via BSEP and ABCB4 signalling pathways. Furthermore, FXR inhibits hepatic reuptake and intestinal absorption via SHP-FXR signalling [31]. Asam ursodeoksikolat adalah salah satu agonis FXR. Ursodeoxycholic acid functions as an FXR agonist. A study conducted in China found evidence that ursodeoxycholic acid may enhance enterohepatic circulation by inhibiting FXR signalling in the ileum and FGF15/19 in the liver. The bilirubin signalling pathway in humans remains poorly understood [32].

In a separate trial, ursodeoxycholic acid shown protective effects for preterm newborns undergoing parenteral nourishment. A randomised experiment in the NICU indicated that newborns administered ursodeoxycholic acid treatment at one week of age exhibited significantly reduced bilirubin levels compared to those who did not receive the medication. Cholestasis was absent in the therapy group (0.0% vs. 11.7%, $p < 0.05$) [33].

Another potential explanation was the duration of ursodeoxycholic acid treatment and the timing of laboratory assessments. A pilot randomised controlled trial administering ursodeoxycholic acid to children with hepatotoxicity from anti-convulsants indicated a substantial reduction in AST and ALT values beginning a week post-administration ($p < 0.001$) [34]. Another research corroborated this finding, concluding that the elevation in total bilirubin and direct bilirubin resulting from cholestasis improved following two weeks of treatment [35].

This study has several limitations that warrant consideration. This research utilised a retrospective cohort design, with data collection conducted over a brief period. This method prevents the evaluation of the causal relationship among the variables. The small annual incidence of cholestasis results in a limited sample size for the study. This study employs a retrospective methodology utilising secondary data, which resulted in challenges in obtaining complete data and a heightened risk of bias. This study was conducted at a tertiary referral hospital. Consequently, identifying cholestasis patients without comorbid conditions necessitating multiple treatments proved challenging in order to mitigate confounding variables. This study did not account for the use of medications other than ursodeoxycholic acid among the subjects, which may introduce bias into the findings. This study provides a detailed examination of changes in liver function biomarker values following the administration of ursodeoxycholic acid, categorising participants into two groups.

5. Conclusion

Ursodeoxycholic acid presents promise in the treatment of cholestasis or as an adjunct therapy in paediatric patients by markedly decreasing bilirubin levels and enhancing liver function. The administration of ursodeoxycholic acid to infant with cholestasis who have not acquired liver fibrosis results in a more favourable outcome. The timely recognition of cholestasis is essential for determining the ideal timing for medication administration.

Funding:
This study received no particular grant from any funding source in the public, commercial, or non-profit sectors.

Authors' Contributions:
NH: data collection, data analysis, conceptualization, drafting, manuscript preparation; BS: supervision, analysis, interpretation; CD: supervision, analysis, editing, interpretation; RA: manuscript preparation, editing

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Edelweiss Applied Science and Technology
ISSN: 2576-8484
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