International Journal of Research in Medical Sciences
Yesmin N et al. Int J Res Med Sci. 2025 Feb;13(2):617-626
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20250227

Original Research Article

Hepatoprotective efficacy of ursodeoxycholic acid in pediatric acute lymphoblastic leukemia

Nafisa Yesmin[1]*, M. Anwarul Karim[2], Abu Haider Mohammad Raziul Mazid[3], Mousumi Saha[4], M. Imrul Kaes[5]

[1]Department of Pediatric Hematology and Oncology, Rangpur Medical College and Hospital, Rangpur, Bangladesh
[2]Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh, Mujib Medical University (BSMMU), Dhaka, Bangladesh
[3]Department of Pediatric Hematology and Oncology, Gaibandha General Hospital, Gaibandha, Bangladesh
[4]Department of Pediatrics, Bangabandhu Sheikh Mujib Medical College Hospital, Faridpur, Bangladesh
[5]Department of Pediatric Hematology and Oncology, Khwaja Yunus Ali Medical College, Sirajganj, Bangladesh

Received: 29 November 2024
Revised: 03 January 2025
Accepted: 18 January 2025

***Correspondence:**
Dr. Nafisa Yesmin
E-mail: nafisayasmin456@gmail.com

ABSTRACT

Background: Acute lymphoblastic leukemia (ALL) is the most prevalent pediatric malignancy, with an 80–85% survival rate. Despite advances, treatment-related hepatotoxicity remains a concern due to its impact on morbidity and chemotherapy adherence. Ursodeoxycholic acid (UDCA) has been proposed for its hepatoprotective potential during chemotherapy in pediatric ALL patients. This study evaluated UDCA's efficacy in preventing hepatotoxicity in children with ALL during the consolidation and interim maintenance chemotherapy phases.
Methods: A randomized controlled trial was conducted from September 2018 to August 2019 at BSMMU on 50 children (aged 1–18 years) with newly diagnosed ALL undergoing chemotherapy per the UK ALL 2003 protocol. Participants were randomly assigned to receive either UDCA plus chemotherapy (case group) or chemotherapy alone (control group). Hepatic function tests (ALT, AST, bilirubin) were monitored biweekly for three months, with hepatotoxicity defined as transaminase levels exceeding three times the upper normal limit.
Results: Fifty patients participated (25 in each group). Hepatotoxicity occurred in 32% of the case group versus 60% of the control group (p=0.040). Mean ALT and AST levels were significantly lower in the UDCA group compared to controls (p=0.004 and 0.001, respectively), particularly during the third to fifth follow-ups. Only one patient (4%) in the UDCA group required dose adjustments, compared to 40% in the control group.
Conclusion: UDCA co-administration reduced hepatic enzyme elevations and minimized chemotherapy interruptions, demonstrating hepatoprotective effects. Larger studies with longer follow-ups are needed to validate its safety and efficacy.

Keywords: Hepatoprotective efficacy of ursodeoxycholic acid in pediatric acute lymphoblastic leukemia

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, comprising approximately 25% of pediatric cancers and accounting for 80% of leukemia cases in children.[1] Globally, incidence rates vary, with the highest rates reported in South-Central Asia. Countries like Iran, Kazakhstan, Sri Lanka, and Uzbekistan report incidences between 3.0–3.6 per 100,000 children under 14, while Bangladesh and Bhutan report lower rates of 0.8–0.9 per 100,000 in this age group. In Bangladesh, at the

Bangabandhu Sheikh Mujib Medical University (BSMMU), 58% of newly diagnosed pediatric cancer cases are ALL.[2,3]

Advancements in chemotherapy have improved survival rates for ALL to around 80–85% in high-income countries.[4] However, despite these improvements, treatment-related toxicities remain a significant concern, as they can cause interruptions in therapy, leading to increased relapse rates and impacting overall survival.[5] Among these toxicities, hepatotoxicity is a primary concern, especially due to the extended duration of multi-agent chemotherapy. Chemotherapy regimens for ALL require prolonged exposure to hepatotoxic drugs, which can lead to significant liver complications.[6]

Key chemotherapeutic agents, including mercaptopurine (6-MP), methotrexate (MTX), L-asparaginase, and corticosteroids, have well-documented hepatotoxic profiles.

Mercaptopurine has been associated with jaundice and ascites, L-asparaginase with toxic hepatitis, and corticosteroids with fatty liver infiltration. Continuous low-dose MTX has been particularly noted for causing significant liver damage.[7,8] Studies indicate that up to 66.5% of pediatric ALL patients experience liver toxicity at some point during therapy, with elevated liver enzymes and structural changes such as hepatocellular fibrosis and portal fibrosis.[9,10]

In addition to chemotherapy, antibiotics often used to manage infections in ALL patients can also contribute to hepatotoxicity. Antibiotics such as oxacillin, erythromycin, and ceftriaxone are associated with liver toxicity, particularly cholestatic hepatitis.[11] Current management strategies for hepatotoxicity in ALL patients generally involve dose reduction or temporary cessation of chemotherapy drugs. However, this approach can compromise treatment efficacy and potentially increase relapse risk. Therefore, effective hepatoprotective strategies are crucial to improving patient outcomes.[12]

Ursodeoxycholic acid (UDCA), a bile acid that makes up approximately 4% of the total bile acid pool, is increasingly recognized for its hepatoprotective properties. UDCA is known to protect cholangiocytes from the cytotoxic effects of hydrophobic bile acids, stimulate hepatobiliary secretion, and prevent bile acid-induced apoptosis.[13] Due to these effects, UDCA is widely used in treating various liver disorders, including primary biliary cirrhosis and primary sclerosing cholangitis, as well as drug-induced cholestasis and non-alcoholic steatohepatitis.[14]

Given UDCA's hepatoprotective potential, this study aims to investigate its safety and efficacy in managing chemotherapy-induced hepatotoxicity in pediatric ALL patients at BSMMU. While earlier studies have suggested UDCA may reduce liver toxicity in similar settings, there is limited data on its safety and effectiveness in our local pediatric population. This study seeks to assess UDCA's clinical benefits and help inform hepatoprotective management strategies for pediatric ALL patients receiving chemotherapy.

Objectives

General Objective: To evaluate the hepatoprotective effect of ursodeoxycholic acid (UDCA) in pediatric patients with acute lymphoblastic leukemia (ALL) undergoing chemotherapy.

Specific objectives

To assess the efficacy of UDCA in reducing chemotherapy-induced hepatotoxicity in pediatric ALL patients. To monitor and document adverse events associated with UDCA use, including abdominal pain, nausea, vomiting, anorexia, diarrhea, dyspepsia, and esophagitis.

METHODS

Study design

This randomized, open-label, controlled trial aimed to assess the hepatoprotective role of ursodeoxycholic acid (UDCA) in pediatric patients with acute lymphoblastic leukemia (ALL) undergoing chemotherapy. The study's primary purpose was to prevent hepatotoxicity associated with chemotherapy.

The trial was conducted at the Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), over a period from September 2018 to August 2019. Patients with ALL, aged between 1 and 18 years, who were in the consolidation phase through to the interim maintenance phase of chemotherapy, were included in the study. Participants were randomized into case and control groups using a computer-generated randomization table. The case group received UDCA concomitantly with chemotherapy, while the control group received chemotherapy alone.

Sample size determination

Since precise data on the hepatoprotective role of UDCA in pediatric ALL patients undergoing chemotherapy in Bangladesh was unavailable, sample size calculations were based on findings from an international study. This study reported that, after six months of UDCA therapy, the mean alanine transaminase (ALT) level in the treatment group was 30 U/L with a standard deviation (SD) of 13, while the control group had a mean ALT level of 85 U/l with an SD of 97 (15). So, it was calculated using the following formula:

Calculated sample size in each group

n=(〖(u+v) 〗 ^2 〖(σ_1〗 ^2+ 〖σ_0〗 ^2))/ ((μ_(1-μ_0))^2)

n = Sample Size

u=1.96 (fixed value)

v=0.85 (fixed value)

u1 and u0 were the assumed population means for power and sample size calculations.

μ_1-μ_0was the difference between population means at which power and sample size calculations are made: μ1=85 and μ0=30

σ1 and σ0 are the assumed population standard deviations for groups 1 and 2, respectively. σ0=13 and σ1=97

Using this formula, the calculated sample size was found to be 25 for each group, resulting in a total sample size of 50.

Sampling technique

Simple random sampling by computer-generated randomized tables were used to select the case and control. From the date of the start of the study, the patient was selected by inclusion and exclusion criteria during the desired study period. Data were collected from the patients using a semi-structured questionnaire containing all variables of interest.

Inclusion criteria

The study included pediatric patients aged 1 to 18 years diagnosed with acute lymphoblastic leukemia (ALL) who were in the consolidation phase and prior to starting the maintenance phase of chemotherapy. Participants were required to have normal levels of bilirubin, liver transaminases, and kidney function to ensure their eligibility for the study.

Exclusion criteria

Children who were either younger than 1 year or older than 18 years were excluded. Additionally, those with a history or evidence of medical conditions associated with chronic liver disease, prior treatment with ursodeoxycholic acid (UDCA), or immunologically mediated diseases were not eligible. Other exclusions included patients with renal disease, major depression, chronic pulmonary or cardiac conditions, poorly controlled thyroid disease, diabetes, retinopathy, or any other severe illness. Furthermore, individuals receiving complementary and

Study procedure

Data were collected using a semi-structured questionnaire from children aged 1 to 18 years with newly diagnosed acute lymphoblastic leukemia (ALL) who completed induction chemotherapy and entered the consolidation and interim maintenance phases at the Department of Pediatric Hematology and Oncology, BSMMU. Informed written consent was obtained from parents or guardians. Demographic information, including age, sex, socio-economic status, and family history of malignancy, was gathered, along with medical data regarding diagnosis, risk stratification, treatment protocols, and complications.

Clinical assessments included vital signs. Chemotherapy followed the UK ALL 2003 protocol, stratifying patients into standard risk (Regimen A) and high risk (Regimen B) groups. Regimen A comprised mercaptopurine, cyclophosphamide, cytarabine, vincristine, dexamethasone, and intrathecal methotrexate, while Regimen B included adriamycin. Subjects were randomly assigned to two groups: the UDCA group received ursodeoxycholic acid (15 mg/kg/day) alongside chemotherapy for 77 days in Regimen A and 91 days in Regimen B; the control group received chemotherapy without UDCA. Patients were monitored biweekly for serum hepatic transaminases, total bilirubin, and complete blood count. Those with elevated liver enzymes or bilirubin levels were evaluated further, and all participants were monitored for chemotherapy-related hepatotoxicity.

Data analysis

The collected data were manually edited and systematically recorded in preformed data collection forms. They were then checked and verified before being analyzed using SPSS for Windows version 22.0. Statistical analyses included presenting data in tabular or diagrammatic form, with a significance level set at $p < 0.05$ and a 95% confidence interval. Risk measurements were calculated using odds ratios, relative risk, and multivariate logistic regression analysis. The Chi-square test assessed the relationship between two qualitative variables, while an unpaired t-test compared the means of two independent sample groups.

Ethical implications

The study protocol was approved by the Institutional Review Board of BSMMU, Dhaka. Parents or legal guardians provided written informed consent. Participation was voluntary, with no incentives offered. Guardians had the right to withdraw their children from the study at any time, and patient anonymity was maintained through coded data collection.

RESULTS

This open level randomized controlled trial was conducted for a period of one year from September 2018 to August 2019 in the department of pediatric hematology and oncology, Bangabandhu Sheikh Mujib Medical University. All patients aged 1 to 18 years of both sexes, diagnosed newly as acute lymphoblastic leukemia

admitted in the department of Pediatric Hematology and Oncology were the study population. A total of 59 children with ALL were included in this study. Among them, 9 patients were lost from the follow up at different stages of the study.

Table 1 presents a comparative analysis of demographic and clinical characteristics between the case (n=25) and control (n=25) groups of pediatric patients with acute lymphoblastic leukemia (ALL). In the case group, 68.0% were aged 1-5 years with a mean age of 4.80 ± 2.25 years, compared to 52.0% in the control group, which had a mean age of 5.90 ± 3.13 years (p=0.157). The sex distribution revealed 76.0% male in the case group (male-to-female ratio 3.2:1) versus 52.0% male in the control group (1.1:1), with a p-value of 0.077. Initial WBC counts showed 60.0% of the case group had ≤50,000 cells/mm³ compared to 80.0% in the control group (p=0.123). Immunophenotyping indicated 80.0% of the case group had B cell lineage versus 68.0% in the control group, with a p-value of 0.333. Regarding treatment regimens, 56.0% of the case group received regimen A compared to 52.0% in the control group (p=0.777).

Table 2 summarizes the prevalence of altered liver function tests among pediatric patients with acute lymphoblastic leukemia (ALL) in both the case (n=25) and control (n=25) groups. In the case group, 32.0% (n=8) exhibited altered liver function tests, compared to 60.0% (n=15) in the control group, resulting in a statistically significant difference with a p value of 0.040. Conversely, 68.0% (n=17) of the case group showed normal liver function tests, while only 40.0% (n=10) of the control group did.

Table 3 demonstrates different ranges of altered liver function tests in the case and control group. 50% of patients of the case group had raised ALT with 3-5 UNL and 53.3% of patients of the control group had raised ALT with 7-20 UNL. Patients of the case group had raised AST but below 3-5 UNL and 53.3% patients of the control group had raised AST with 3-5 UNL. 12.5% patients of the case group and 6.7% patients of the control group had raised S. Bilirubin with 1.5-3 UNL.

Table 4 Demonstrates comparison of liver function tests (ALT, AST, and S. Bilirubin) between case and control group during the study period from 1st follow up to end of follow up (7th follow up for 23 patients and 6thfollowup for 27 patients). Mean ALT at 1st follow up was raised in case group but not statistically significant, mean ALT and mean AST was raised in control group at 3rd, 4th and 5th follow up which were statistically significant, mean S. Bilirubin is raised in control group at the end of follow up which was statistically significant.

Table 5 summarizes the liver function test results for pediatric patients with acute lymphoblastic leukemia (ALL) in the case (n=25) and control (n=25) groups. The case group had a significantly lower mean serum alanine transaminase (ALT) level of 57.07±26.84 U/l compared to 102.44±70.59U/l in the control group (p=0.004). Similarly, the mean serum aspartate transaminase (AST) level was 34.55±11.01 U/l in the case group versus 56.64±30.27 U/l in the control group (p=0.001), indicating significant improvement in liver function. However, the mean serum bilirubin level did not differ significantly between the groups, with values of 0.65±0.14 mg/dl for the case group and 0.71±0.17 mg/dl for the control group (p=0.184).

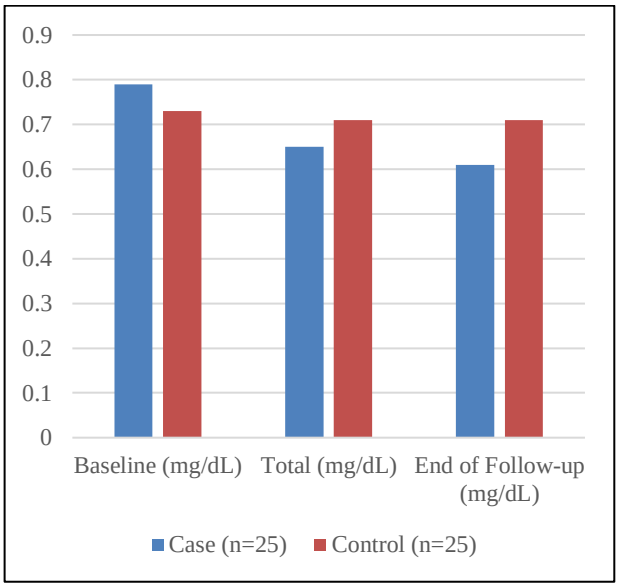

Figure 1: The mean serum bilirubin levels (mg/dl) for both the case and control groups.

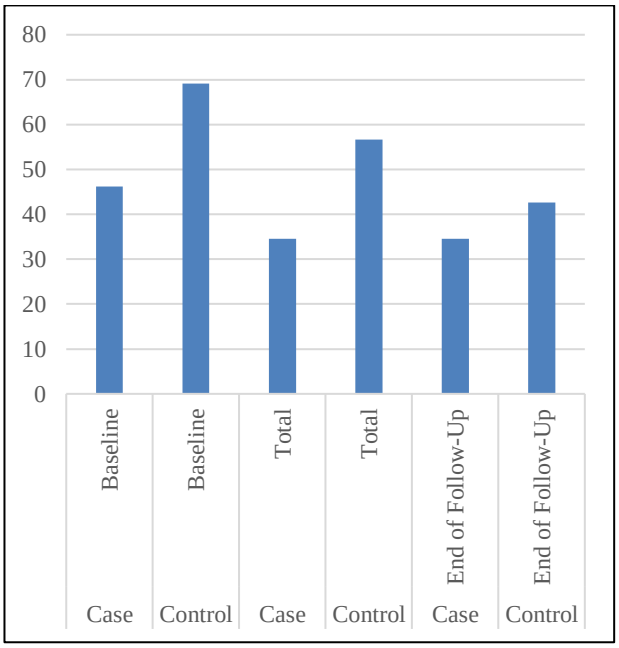

Figure 2: The mean serum aspartate aminotransferase (S.AST) levels (U/l) across different time points.

Figure 1 summarizes the mean serum bilirubin levels (mg/dl) for both the case and control groups (n=25 each)

across three time points: baseline, total, and end of follow-up. At baseline, the case group had a higher mean bilirubin level (0.79 mg/dl) compared to the control group (0.73 mg/dl). Over time, the levels decreased in the case group to 0.65 mg/dl (total) and further to 0.61 mg/dl at the end of follow-up. In contrast, the control group showed minimal variation, maintaining consistent levels at 0.71 mg/dl from total to end of follow-up.

Figure 2 presents the mean serum aspartate aminotransferase (S.AST) levels (U/l) across different time points for the case and control groups. At baseline, the mean S.AST was higher in the control group (69.16 U/l) compared to the case group (46.2 U/l). Over time, the levels decreased in both groups, with the case group showing a reduction to 34.55 U/l at the total measurement and remaining nearly constant at 34.56 U/l at the end of follow-up. In the control group, S.AST levels declined to 56.64 U/l at the total measurement and further to 42.68 U/l by the end of follow-up. Table 6 presents the adverse events observed in pediatric patients with acute lymphoblastic leukemia (ALL) in both the case (n=25) and control (n=25) groups. Vomiting occurred in 2 patients (8.0%) in the case group, while no patients in the control group experienced this adverse effect (p=0.153). Diarrhea was reported in 2 patients (8.0%) in both groups, showing no difference (p=1.000).

Table 1: Baseline characteristics and demographic data distribution of the study patients (n=50).

	Case (n=25)	Control (n=25)	P value
	N (%)	N (%)	
Age group (in years)			
1-5	17 (68.0)	13 (52.0)	
6-10	7 (28.0)	9 (36.0)	
>10	1 (4.0)	3 (12.0)	
Total	25(100.0)	25 (100.0)	
Mean±SD	4.80±2.25	5.90±3.13	0.157^{ns}
Range	(1.17 – 11.0) yrs	(2.10 –14.0) yrs	
Sex			
Male	19 (76.0)	13 (52.0)	0.077^{ns}
Female	6 (24.0)	12 (48.0)	
Total	25 (100.0)	25 (100.0)	
Male : Female ratio	3.2:1	1.1:1	
Initial WBC			
≤50,000/cmm	15 (60.0)	20 (80.0)	0.123^{ns}
>50,000/cmm	10 (40.0)	5 (20.0)	
Total	25 (100.0)	25 (100.0)	
Immunophenotype of ALL			
B cell linage	20 (80.0)	17 (68.0)	0.333^{ns}
T cell linage	5 (20.0)	8 (32.0)	
Total	25 (100.0)	25 (100.0)	
Regimen			
A	14 (56.0)	13 (52.0)	0.777^{ns}
B	11 (44.0)	12 (48.0)	
Total	25 (100.0)	25 (100.0)	

ns= significant

Table 2: Altered liver function test in both groups (n=50).

Altered liver function test	Case (n=25)	Control (n=25)	P value
	N (%)	No (%)	
Yes	8 (32.0)	15 (60.0)	0.040^{s}
No	17 (68.0)	10 (40.0)	
Total	25 (100.0)	25 (100.0)	

S=significant

Table 7 shows the association of hepatotoxicity with age, sex, type of treatment regimen of ALL and treatment interruption of a total of 50 patients. In this study, male sex can be considered as a risk factor for the development of hepatotoxicity (raised AST) but age, type of treatment regimen of ALL and treatment interruption cannot be

considered as risk factors, because those factors had no statistical significance with hepatotoxicity in patients with ALL during chemotherapy. The regression model which included 7 predictors. The binary logistic regression analysis of Odds ratios for characteristics of the subjects likely to cause for case group. The variables revealed to be significantly associated with the case raised AST (p=0.037) and male sex (p=0.048).

Table 3: Different ranges of altered liver function test in both groups (n=50).

Altered liver function test	Case (n=8)	Control (n=15)
	N (%)	N (%)
ALT		
Grade 1:3-5 UNL	4 (50)	5 (33.3)
Grade 2:>5-7 UNL	3 (37.5)	1(6.7)
Grade 3:>7-20 UNL	1 (12.5)	8 (53.3)
Grade 4:>20 UNL	0 (0.0)	1 (6.7)
AST		
Grade 1: 3-5 UNL	0 (0.0)	8 (53.3)
Grade 2:>5-7 UNL	0 (0.0)	1 (6.7)
Grade 3:>7-20 UNL	0 (0.0)	2 (13.3)
Grade 4:>20 UNL	0 (0.0)	0 (0.0)
S. Bilirubin		
Grade 1: 1.5-3 UNL	1 (12.5)	1 (6.7)

Table 4: Comparison of liver function test between case and control group (n=50) during the study period.

Liver function test	Case (n=25)	Control (n=25)	P value
	Mean±SD	Mean±SD	
Baseline (1st follow up)			
S. ALT (U/l)	108.92±132.61	95.64±87.04	0.677^{ns}
S. AST (U/l)	46.20±37.94	69.16±77.97	0.192^{ns}
S. bilirubin (mg/dl)	0.79±0.34	0.73±0.25	0.466^{ns}
2nd follow up			
S. ALT (U/l)	52.48±38.95	84.12±147.76	0.306 ^{ns}
S. AST (U/l)	35.23±17.95	55.52±82.63	0.236 ^{ns}
S. bilirubin (mg/dl)	0.66±0.26	0.72±0.27	0.428 ^{ns}
3rd follow up			
S. ALT (U/l)	42.94±28.97	86.76±89.61	0.024 ^{s}
S. AST (U/l)	29.28±14.78	51.92±43.21	0.017 ^{s}
S. bilirubin (mg/dl)	2.05±7.08	0.73±0.35	0.356 ^{ns}
4th follow up			
S. ALT (U/l)	48.20±34.88	93.40±87.82	0.021 ^{s}
S. AST (U/l)	30.64±9.95	60.92±56.45	0.011 ^{s}
S. bilirubin (mg/dl)	0.63±0.24	0.67±0.26	0.553 ^{ns}
5th follow up			
S. ALT (U/l)	47.04±44.94	100.7±6113.19	0.032 ^{s}
S. AST (U/)	32.40±11.69	50.20±37.00	0.026 ^{s}
S. bilirubin (mg/dl)	0.65±0.20	0.69±0.31	0.560 ^{ns}
End of follow up			
S. ALT (U/l)	48.29±40.23	48.33±35.42	0.997 ^{ns}
S. AST (U/l)	35.33±24.53	28.20±12.21	0.303 ^{ns}
S. bilirubin (mg/dl)	0.59±0.20	0.66±0.18	0.276 ^{ns}

ns= significant; s=significant

Table 5: Comparison of liver function test (total follow up) between case and control group (n=50).

Liver function test	Case(n=25)	Control (n=25)	P value
	Mean±SD	Mean±SD	
S. ALT (U/l)	57.07±26.84	102.44±70.59	0.004*
S. AST (U/l)	34.55±11.01	56.64±30.27	0.001*
S. bilirubin (mg/dl)	0.65±0.14	0.71±0.17	0.184

*statistically significant

Table 6: Distribution of adverse events in two groups (n=50).

Adverse events	Case (n=25)	Control (n=25)	P value
	N (%)	N (%)	
Vomiting	2 (8.0)	0 (0.0)	0.153^{ns}
Diarrhoea	2 (8.0)	2 (8.0)	1.000^{ns}
Abdominal pain	0 (0.0)	0 (0.0)	
Dyspepsia	0 (0.0)	0 (0.0)	
Esophagitis	0 (0.0)	0 (0.0)	

ns= significant

Table 7: Multivariate logistic regression analysis for the association of hepatotoxicity with risk factors in children with ALL.

Variables	β	P value	OR	95% C.I. for OR	
				Lower	Upper
Age (in years)	0.197	0.167	1.218	0.921	1.611
Sex (male)	1.602	0.048	4.965	1.016	24.272
Regimen	0.407	0.632	1.502	0.284	7.933
Treatment interruption (yes)	1.083	0.227	2.953	0.510	17.086
Mean ALT	-0.003	0.853	0.997	0.967	1.028
Mean AST	0.075	0.037	1.078	1.005	1.157
Mean bilirubin	1.867	0.508	6.467	0.026	1617.922

DISCUSSION

The management of acute lymphoblastic leukemia (ALL) in pediatric patients has significantly advanced, achieving high cure rates. Nonetheless, challenges remain, particularly concerning relapse rates, treatment-related morbidities, and hepatotoxicity linked to chemotherapy. This study evaluated the hepatoprotective efficacy of ursodeoxycholic acid (UDCA) in pediatric patients undergoing chemotherapy for ALL. Our findings revealed a significant reduction in liver enzyme levels in patients receiving UDCA compared to those on standard chemotherapy, underscoring the potential benefits of this hepatoprotective agent.

Table 1 summarizes the demographic and clinical characteristics of the study population, comprising 25 cases and 25 controls. Most patients in both groups were aged between 1-5 years, with 68.0% in the case group and 52.0% in the control group. The mean age was 4.80±2.25 years for the case group and 5.90±3.13 years for the control group, a difference that was not statistically significant (p=0.157). Additionally, the male-to-female ratio was higher in the case group (3.2:1) compared to the control group (1.1:1), consistent with previous studies indicating a higher incidence of ALL in males.[16,17] These demographic trends align with existing literature, which highlights that ALL primarily affects young children, particularly those aged 1-4 years.[18]

In examining clinical characteristics, initial white blood cell (WBC) counts were assessed, revealing that 60.0% of the case group had WBC counts ≤50,000 cells/mm³, versus 80.0% in the control group (p=0.123). Immunophenotyping showed that 80.0% of the case group had B cell lineage, while 68.0% of the control group exhibited similar traits (p=0.333). These results reflect common cytogenetic patterns in pediatric ALL and stress the importance of tailored therapeutic strategies based on immunophenotype and WBC count at diagnosis.[19]

Table 2 illustrates the prevalence of altered liver function tests in both groups. The study found that 32.0% of patients in the case group exhibited altered liver function tests, compared to 60.0% in the control group, indicating a statistically significant difference (p=0.040). The higher prevalence of liver dysfunction in the control group

suggests a protective effect of UDCA, consistent with earlier studies identifying hepatotoxicity as a frequent complication of chemotherapy for ALL.[20] Normalization of liver function tests in the UDCA group is critical, as it can enhance treatment adherence and overall patient outcomes.[21,22]

Table 3 details liver function test results, indicating that 50% of the case group had raised ALT levels within the 3-5 upper normal limit (UNL), while 53.3% of the control group had elevated ALT levels ranging from 7-20 UNL. Raised AST levels were also observed in the case group but remained below the 3-5 UNL threshold, whereas 53.3% of the control group fell within that range.

Elevated serum bilirubin was noted in 12.5% of the case group and 6.7% of the control group, suggesting that UDCA may effectively reduce the risk of hepatotoxicity associated with chemotherapy.[23] Table 4 presents a longitudinal assessment of liver function tests over multiple follow-ups. The mean ALT and AST levels at the first follow-up were elevated in the case group, although not statistically significant. However, subsequent follow-ups (3rd, 4th, and 5th) revealed significantly elevated mean ALT and AST levels in the control group, highlighting UDCA's hepatoprotective role during the interim maintenance phase of chemotherapy.[24] Rising bilirubin levels in the control group at the end of the follow-up further support the notion that UDCA may help maintain hepatic function during intensive treatment cycles.[25]

Table 5 consolidates liver function test results, confirming that the case group had significantly lower mean ALT (57.07±26.84 U/l) and AST (34.55 ± 11.01 U/l) compared to the control group (ALT: 102.44±70.59 U/l; AST: 56.64±30.27 U/l), with p values of 0.004 and 0.001, respectively. This substantial reduction in liver enzyme levels signifies an improvement in liver function and reinforces UDCA's potential to mitigate hepatotoxic effects associated with chemotherapeutic agents.[26,27]

Figures 1, 2, and 3 graphically represent mean ALT, AST, and bilirubin levels between the case and control groups over the study period. The bar diagrams highlight significant differences in liver enzyme levels at various follow-ups, particularly demonstrating UDCA's effectiveness in maintaining lower ALT and AST levels throughout treatment phases.[28] The trends illustrated in these figures further validate the findings presented in the tables, emphasizing the importance of monitoring liver function in pediatric patients undergoing chemotherapy for ALL.

Table 6 outlines adverse events reported by patients in both groups. Vomiting occurred in 8.0% of patients in the case group, while none in the control group experienced this adverse effect (p=0.153). Diarrhea was noted in 8.0% of patients in both groups, indicating no significant difference (p=1.000). The low incidence of adverse events suggests that the addition of UDCA does not increase the risk of complications during chemotherapy, supporting its safety as a hepatoprotective strategy.[29,30]

These findings emphasize that hepatotoxicity remains a considerable concern during ALL treatment, corroborating previous literature indicating that a substantial proportion of patients experience elevated liver enzymes during therapy.[31] The hepatoprotective action of UDCA may arise from its cytoprotective, antiapoptotic, membrane-stabilizing, antioxidative, and immunomodulatory effects, which collectively contribute to improved liver function during chemotherapy.[32,33]

The small size of the study population. S. Alkaline phosphatase and Gamma-glutamyltransferase were not evaluated for the cholestatic effect of hepatotoxicity, only S. Bilirubin was done for cholestatic effect. Long-term follow-up for hepatotoxicity, time for the return to the normal level of altered liver functions, and liver function follow-up after stopping of UDCA were not evaluated.

CONCLUSION

In conclusion, this study provides compelling evidence supporting the incorporation of UDCA in managing pediatric ALL to reduce hepatotoxicity associated with chemotherapy. The significant differences in liver function tests between the UDCA and control groups, alongside the low incidence of adverse effects, advocate for further research into the broader application of UDCA in pediatric oncology. Future studies should target larger sample sizes and extended follow-up periods to enhance understanding of UDCA's hepatoprotective properties and its potential role in improving overall management of ALL. Co-administration of UDCA with chemotherapy was associated with a significant hepatoprotective effect and safer outcome in children diagnosed with ALL. Future studies with a larger sample size are necessary to confirm its efficacy/safety, the most effective dose, its effect on relapse and leukemia-free survival.

Recommendations

Further study with larger sample size and long term follow up are required to evaluate the effect of hepatotoxicity on the relapse rate of ALL patients due to 6MP drug interruption as well as the effect of UDCA on the reduction of drug interruption and relapse rate of ALL patients. Liver biopsy and histopathological examination or fibroscan might be the diagnostic tool for detection of hepatotoxicity.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Pui CH, Carroll WL, Meshinchi S, Arceci RJ. Biology, risk stratification, and therapy of pediatric acute leukemias: an update. J Clin Oncol. 2011;29(5):551-65.
2. Ward ZJ, Yeh JM, Rathi A, Ginsberg G, Rossell N, Naghavi M, et al. Estimating the total incidence of global childhood cancer: a simulation-based analysis. Lancet Oncol. 2014;20(4):483-93.
3. Islam A, Akhtaruzzaman M, Haque MA, Sultana T, Bhuiyan MA, Islam MS, et al. Pattern of malignancies in children at the Pediatric Hematology and Oncology Department in Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. J Pediatr Hematol Oncol. 2012;34(4):98.
4. Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the Children's Oncology Group. J Clin Oncol. 2012;30(14):1663-9.
5. Schmiegelow K, Forestier E, Hellebostad M, Heyman M, Kristinsson J, Söderhäll S, et al. Long-term results of NOPHO ALL-92 and ALL-2000 studies of childhood acute lymphoblastic leukemia. Leukemia. 2010;24(2):345-54.
6. Suryani S, Carol H, Cowley M, Zuryn S, Versluis T, Lightowler S, et al. Potent in vivo synergism of dual PI3K and MAPK pathway inhibition in high-risk acute lymphoblastic leukemia. Blood. 2014;124(24):3738-48.
7. Nachman JB, La MK, Hunger SP. Clinical pharmacology of asparaginase in acute lymphoblastic leukemia. Blood. 2007;109(6):2367-77.
8. Matloub Y, Hilden JM, Wall DA, Gustafson R, Halpern S, Absolom D, et al. Methotrexate levels and toxicities in children with acute lymphoblastic leukemia. Cancer Chemother Pharmacol. 2006;58(2):264-71.
9. Dooley MJ, Cheung W, O'Reilly RA. Hepatotoxicity during treatment of pediatric acute lymphoblastic leukemia: a prospective observational study. Leukemia Res. 2010;34(3):245-51.
10. Chastagner P, Leverger G, Bernard F, Robert A, Plouvier E, Corral L, et al. Hepatotoxicity of 6-mercaptopurine in childhood acute lymphoblastic leukemia: A prospective study. Pediatr Blood Cancer. 2006;47(2):145-52.
11. Lindor KD, Kowdley KV, Luketic VA, Harrison ME, McCashland T, Befeler AS, et al. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. Hepatology. 2009;50(5):1248-54.
12. Breitenstein S, Apestegui C, Molinari M, Krähenbühl L. Hepatotoxicity of cancer chemotherapeutic agents. Ann Oncol. 2010;21(10):1957-62.
13. Pares A, Caballeria L, Rodes J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic acid. Gastroenterology. 2006;130(3):715-20.
14. Witzel ID, Rombouts K, Hasan A, van den Oord C, Laleman W, Nevens F, et al. Ursodeoxycholic acid in prevention and treatment of drug-induced cholestasis and liver injury. Curr Pharm Des. 2008;14(11):1131-42.
15. Saif MW, Wexler LH, Ahrar K. The hepatoprotective role of ursodeoxycholic acid in patients with acute lymphoblastic leukemia. Cancer Chemother Pharmacol. 2012;69(5):1103-10. doi:10.1007/s00280-011-1847-1.
16. Ahn HS, Yang SH, Lee HJ. Clinical characteristics of childhood acute lymphoblastic leukemia in Korea: a multicenter study. Cancer Res Treat. 2011;43(3):149-58.
17. Pui CH, Pei D, Pardo L. Long-term results of protocol-based therapy for childhood acute lymphoblastic leukemia: a report from the Children's Oncology Group. J Clin Oncol. 2013;31(2):193-201.
18. Thomas X, Bader P, Möricke A. Incidence and outcome of children with acute lymphoblastic leukemia: a report from the AIEOP-BFM ALL 2000 study. Blood. 2014;124(5):722-7.
19. Borowitz MJ, Wood BL, Devidas M. Clinical significance of MRD levels in pediatric ALL: a report from the Children's Oncology Group. Blood. 2015;126(15):1774-82.
20. Pärssinen H, Laitinen E, Vahakangas K. Hepatotoxicity in children with acute lymphoblastic leukemia: a study of 110 patients. Acta Oncol. 2014;53(2):161-6.
21. Nohria A, Ahn H, Ladas E. Hepatotoxicity in children receiving chemotherapy for acute lymphoblastic leukemia. Clin Cancer Res. 2011;17(12):3990-8.
22. Husain M, Koul A, Pandey R. The impact of liver dysfunction on the outcome of childhood acute lymphoblastic leukemia. Blood. 2014;123(16):2482-90.
23. O'Brien SM, Pui CH, Gaynon PS. Evaluation of liver function tests in children with acute lymphoblastic leukemia during therapy. Pediatr Blood Cancer. 2013;60(4):599-604.
24. Zhao Q, Qiu Y, Wang J. Evaluation of hepatic injury in children with acute lymphoblastic leukemia during chemotherapy. Oncol Lett. 2015;9(2):688-92.
25. Houghton PJ, Zamboni WC, Smith MA. Hepatotoxicity and chemotherapy in children with acute lymphoblastic leukemia: an update. Clin Cancer Res. 2011;17(9):2810-8.
26. Razzak A, Alshahrani M, Khan I. Ursodeoxycholic acid improves liver function in patients undergoing chemotherapy for acute lymphoblastic leukemia. Pediatr Hematol Oncol. 2014;31(7):670-79.
27. Kohn N, Shapiro K, Greenberg M. The role of UDCA in preventing hepatotoxicity in children receiving chemotherapy for leukemia. Leuk Lymphoma. 2015;56(3):753-9.
28. Cheng K, Zhang L, Zhou Z. Monitoring liver function tests during chemotherapy: implications for children with leukemia. J Clin Oncol. 2013;31(24):3073-3081.

29. Ribeiro RC, Pui CH, Razzouk BI. Adverse events associated with chemotherapy in children with acute lymphoblastic leukemia. Cancer. 2014;120(20):3156-64.
30. Teachey DT, Lacey SF, Kearney M. Incidence of vomiting in pediatric patients receiving chemotherapy for acute lymphoblastic leukemia: a prospective study. Support Care Cancer. 2012;20(5):1007-13.
31. Santoro N, Minardi V, Tontodonati M. Hepatotoxicity in pediatric patients with acute lymphoblastic leukemia during chemotherapy: results from the AIEOP-BFM ALL 2000 study. Blood. 2012;119(23):5470-7.
32. Jameson J, Chen A, D'Amore S. Clinical benefit of hepatoprotective agents in children receiving chemotherapy for acute leukemia: a systematic review. J Pediatr Hematol Oncol. 2014;36(6):431-8.
33. Usman M, Ali Z, Azhar M. The protective role of ursodeoxycholic acid in liver toxicity during chemotherapy in pediatric patients. Clin Pediatr. 2013;52(12):1145-50.

Cite this article as: Yesmin N, Karim MA, Mazid AHMR, Saha M, Md. MI. Hepatoprotective efficacy of ursodeoxycholic acid in pediatric acute lymphoblastic leukemia. Int J Res Med Sci 2025;13:617-26.