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Hepatoprotective Efficacy of Ursodeoxycholic Acid in Childhood Acute Lymphoblastic Leukemia (ALL) in a Tertiary Care Hospital

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Abstract

Background*: Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy.There are many successful treatment regimens for ALL. The chemotherapeutic agents used in the treatment of ALL are potentially hepatotoxic. Ursodeoxycholic acid (UDCA) has some role in preventing chemotherapy induced hepatotoxicity. The study was done to find out the hepatoprotective efficacy of UDCA in childhood ALL.*

Materials &Methods*: This was a quasi-experimental study conducted in the department of Paediatric Haematology and Oncology, Dhaka Medical College Hospital, Dhaka. A total of 35 patients diagnosed as ALL were randomized in two groups.One group got UDCA along with chemotherapy and the other group chemotherapy alone. Estimation of S. ALT, S. AST and S. bilirubin were done before and after 1st,2nd,3rd and 4th week of starting chemotherapy.*

Result*: The mean levels of S. ALT and S. AST were higher in the group that did not get UDCA. There were significant differences between S. ALT and S. AST level after 4th weeks of starting chemotherapy. However, S. bilirubin level was almost similar in both groups.*

Conclusion*: UDCA showed hepatoprotective efficacy in induction period of chemotherapy.*

Key words*: Acute Lymphoblastic Leukemia (ALL), Ursodeoxycholic acid (UDCA), hepatoprotective efficacy*

Introduction:

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy.[1] Among children with ALL, 10 years event free survival is about 90% with current treatment protocols that incorporate systemic combination chemotherapy with or without cranial radiation.[2] There are many successful treatment regimens for ALL. All the ALL regimens include certain treatment elements: induction of remission, consolidation (intensification of remission), central nervous system (CNS) prophylaxis and maintenance therapy. Remission induction with three or four drugs (i.e., vincristine, dexamethasone, L-asparaginase, intrathecal chemotherapy with or without anthracyclines) depending on the risk classification. Combination chemotherapy uses several chemotherapeutic agents, each with a different mechanism of action and toxicity profile. [3,4]

Along with the potential for greater tumor kill, however, the possibility for enhanced toxicity occurs. Many of the agents used in the treatment of ALL are potential hepatotoxins.[5] These chemotherapeutic drugs cause elevation of the hepatic enzymes along with hyperbilirubinemia, which becomes normal after stopping the chemotherapy for the time being. But withholding the chemotherapy results in relapse or treatment failure of ALL patients.[6-8] Ursodeoxycholic acid (UDCA) is a dihydroxy bile acid, which constitutes 4% of total bile acid pool. Due to its beneficial effects on the liver, UDCA is widely used in chronic cholestatic diseases such as primary biliary cirrhosis, primary sclerosing cholangitis, drug-induced cholestasis;

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sometimes in noncholestatic syndromes such as nonalcoholic steatohepatitis, alcoholic steatohepatitis, graft versus host disease and sometimes in autoimmune hepatitis. UDCA is already known to have a cytoprotective role on cholangiocytes by preventing the toxic side effects of other hydrophobic bile acids. UDCA also improves the defective natural killer cell activity by inhibiting prostaglandin E2 synthesis and reduces peripheral eosinophilia.[9,10] UDCA has been shown to induce endogenous antioxidant defenses in rat hepatocytes and to counteract deoxycholate related lipid peroxidation in cultured macrophages and liposomes indicating an indirect type drug antioxidant activity.[11,12] UDCA has direct and significant antioxidant properties, which are relevant against Fe3+ and OH- dependent bimolecular oxidative damage; these properties are evident at therapeutically relevant concentration suggesting that UDCA could act as an antioxidant in vivo.[13] UDCA has been shown to suppress the extent of hepatic lipid peroxidation in experimental cholestatic liver disease, which is characterized by enhanced OH- generation.[14] Due to this hepatoprotective efficacy of UDCA, it has been proposed and sometimes used to prevent the hepatic therapeutic agents used in the treatment of ALL.[15]

Materials and Methods

This Quasi-experimental study was done in the department of PaediatricHaematology and Oncology, Dhaka Medical College Hospital, Dhaka from January 2016 to December 2016. The sample size was 35. They were newly diagnosed as ALL and were undergoing induction of remission. Samples were selected consecutively. The patients with relapse of ALL with co-morbidity, as for example, with heart disease, chronic liver disease, renal disease and who were hypersensitive to UDCA were excluded from the study. Ethical approval was taken from local ethical review board and informed written consent was taken from the guardians or caregivers of the all diagnosed ALL patients. ALL was diagnosed on the basis of clinical features, complete blood counts with peripheral blood film and confirmed by bone marrow study along with immunophenotyping. Some sociodemographic and clinical data of the patients were collected by history taking and physical examination in a structured form. Two ml of venous blood was collected before chemotherapy in a test tube for estimation of serum ALT, AST and total bilirubin by Biolis 24i, (Japan) analyzer. Randomized selection in two group was done by lottery method. UDCA 10mg/kg/day was added in divided doses with meals along with the standard chemotherapy throughout the induction phase (UKALL, 2003 revised protocol) in the case group and only chemotherapeutic agents were continued during induction phase in the control group.Serum ALT, AST and total bilirubin were monitored weekly during the induction phase of chemotherapy in both case and control groups.Chemotherapy was stopped if there was elevation of hepatic enzymes ten times or more of upper limit of normal in both case and control groups. Chemotherapy was restarted when hepatic enzymes returned to two times of its upper normal limit. The variation of changes among the case and control groups and the changing profile with chemotherapeutic agents were obtained from the data that were recorded in structured questionnaire. Statistical analyses were carried out by using the Statistical Package for Social Sciences version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

Most of the patients were at the age range of 0 to 5 years (16/35). Among the total 35 patients 22 (62.9%) were male and 13 (37.1%) were female (Table I). Among them 17/35 were given UDCA along with chemotherapy and 18/35 chemotherapy alone (Figute-1).

Table I

Age & sex distribution of study population(n=35)

	Frequency(%)
Age	
0 to 5 years	16 (45.7%)
5 to 10 years	13 (37.1%)
>10 years	6 (17.2%)
Sex	
Male	22 (62.9%)
Female	13 (37.1%)

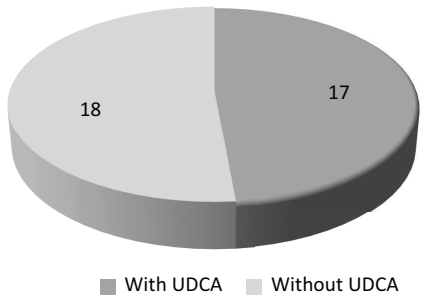

Figure-1: *Showing two group of study population (n=35)*

Before starting the chemotherapy, the mean S. ALT level of the group that got UDCA was 26.05±24.54 and in the group which did not get UDCA was 35.55±36.92. The difference was not statistically significant. Comparing the S. ALT value between two groups after 1st, 2nd and 3rd weeks no significant difference was found at any stage. Then again after the 4th week the respective value was 48.86±32.00 and 125.05±103.73 in UDCA and nonUDCA group. The difference was statistically significant (p<0.05). Mann-Whitney U test was applied as tool for statistical analysis (Table II).

Before starting the chemotherapy, the mean S. AST level of the group that got UDCA was 22.37±9.63 and in the group which did not get UDCA was 22.94±13.22. The difference was not statistically significant. Comparing the S. AST value between two groups after 1st, 2nd and 3rd weeks no significant difference was found at any stage. Then again after the 4th week the respective value was 24.53±12.69 and 39.53±20.56 in UDCA and nonUDCA group. The difference was statistically significant (p<0.05) (Table III).

Before starting thechemotherapy,the mean S. Bilirubin level of the group that got UDCA was 0.42±0.20 and in the group that did not get UDCA was 0.38±0.21 which was statistically non-significant. Comparing the S. Bilirubin data between two groups after 1st, 2nd. 3rd and 4th weeks no significant difference was found at any stage (Table V). After the 4th week of chemotherapy abnormal S. ALT was found in 6 patients in UDCA group and 14 patients in non-UDCA group (p value was <0.05). The difference between number of patients with abnormal S. AST and S. bilirubin in the two groups were statistically non-significant(Table IV).

Table II

Estimation of serum ALT before and after starting of chemotherapy

S. ALT	Category	Mean S.ALT	SD	P value
Baseline	with UDCA	26.05	24.54	0.19
	without UDCA	35.55	36.92	
After 1 wk	with UDCA	41.64	39.91	0.06
	without UDCA	73.66	75.14	
After 2 wk	with UDCA	58.94	53.44	0.42
	without UDCA	77.44	73.08	
After 3 wk	with UDCA	61.41	57.94	0.10
	without UDCA	73.88	35.50	
After 4 wk	with UDCA	48.86	32.00	0.008*
	without UDCA	125.05	103.73	

Table III

Estimation of serum AST before and after starting of chemotherapy.

S. AST	Category	Mean	SD	P value
At baseline	with UDCA	22.37	9.63	0.40
	without UDCA	22.94	13.22	
After 1wk	with UDCA	25.76	7.27	0.31
	without UDCA	27.72	18.63	
After 2 wk	with UDCA	36.88	25.73	0.40
	without UDCA	33.72	30.51	
After 3 wk	with UDCA	29.11	13.44	0.52
	without UDCA	30.38	11.32	
After 4 wk	with UDCA	24.53	12.69	0.004*
	without UDCA	39.35	20.56	

Table IV

Estimation of serum bilirubin before and after starting chemotherapy.

S. Bilirubin	Category	Mean	SD	P value
Baseline	with UDCA	0.42	0.20	0.50
	without UDCA	0.38	0.21	
After 1 wk	with UDCA	0.58	0.24	0.59
	without UDCA	0.69	0.44	
After 2 wk	with UDCA	0.76	0.48	0.30
	without UDCA	0.65	0.39	
After 3 wk	with UDCA	0.57	0.16	0.93
	without UDCA	0.59	0.24	
After 4 wk	with UDCA	0.56	0.18	1.00
	without UDCA	0.74	0.65	

Table V

Number of patients with abnormal level of serum ALT, AST and bilirubin after 4th week of chemotherapy

After 4thweek of chemotherapy	UDCA group (n=17)	Non-UDCA group (n=18)	p value
Abnormal S. ALT(S. ALT>45)	6	14	0.01
Abnormal S. ASTS. AST>45	2	3	0.67
Abnormal S. bilirubinS. bilirubin> 1.2	1	3	0.31

Discussion:

The mean age of the respondent was 6.01±2.93 years which was pretty similar to the average age of presentation of the childhood ALL.[1] Among them most of the children (82.8%) were up to the age of 10 years (29 of total 35). There was sex variation among the respondents. Among them male and female were 22 and 13 respectively, which corresponded to previous studies.[16] S. ALT level was estimated before and after starting of chemotherapy. The trends of result showed that it was increasing in both groups after starting chemotherapy. But the rising trend was more in the group that did not get UDCA along with chemotherapy. Baseline and after 1st, 2nd and 3rd week of chemotherapy the change between two groups were statistically non-significant. But after the 4th week, the difference was significant (p value=0.008). Many of the chemotherapeutic agents used for the treatment of ALL have hepatotoxic activity.[5] S. ALT is a good indicator to see the hepatic dysfunction. Here in this study the significant rise of S. ALT in the group not receiving UDCA proved the statement. But in the group that received UDCA along with standard chemotherapy had less rise in S. ALT level. After the 4th week of chemotherapythe mean value of S. ALT in the UDCA group was 48.86±32.00 and 125.05±103.73 in non-UDCA group. The difference was statistically significant (p=0.008). This result showed that UDCA had hepatoprotective activity. A study done by MM. Saif et al. in 2012 in Egypt also showedthat S. ALT level was significantly lower in consolidation chemotherapy in ALL children after 6 months who got UDCA.[15] In another study at Dhaka Shishu Hospital, UDCA reduced SGPT in 15 patients(75%) among 20 cases which is similar to the present study.[16]

Here in this study there was no significant rise in S. AST level after starting the chemotherapeutic agents. However, after the 4th week of chemotherapy there was significant rise in the level of it in the non-UDCA group. So here UDCA also showed some hepatoprotective efficacy. S. bilirubin showed almost equal trend in the study. After the 1st, 2nd, 3rd and 4th week there was no significant rise in the level of S. bilirubin. The result is similar to that found in the previous study of Yamazaki K et al.[9]

After the 4th week of chemotherapy abnormal liver function test was found in both groups. S. ALT was

found abnormal in 6 in 17 patients in UDCA group and it was 14 in 18 patients in non-UDCA group. Suleyman U et al. also found cytoprotective role of UCDA on cholangiocytes by preventing the toxic side effects of other hydrophobic bile acids.[10] It has been proved in different trials that UDCA has hepatoprotective efficacy.[10,11,15,16]

Conclusion

It could be concluded that simultaneous administration of ursodeoxycholic acid (UDCA) along with chemotherapy acts as an effective hepatoprotective agent against chemotherapy induced liver dysfunction.

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