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"Protective effects of ursodeoxycholic acid on chemotherapy-induced hepatic injury in acute leukemia patients: A study in Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh"

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Introduction*: Acute leukemia cases are increasing day by day. Though etiology is not fully known but with appropriate chemotherapy majority cases are cured. During treatment in some cases liver function especially SGPT becomes high, as a result continuation of treatment becomes difficult.*
Objective: *This study aimed to determine the effectiveness of ursodeoxycholic acid for reduction of SGPT in Acute leukemia patients during treatment for continuation of treatment.*
Methods: *This was a prospective cross-sectional study done in Dhaka Shishu (Children) Hospital. We include the patients of acute leukemia admitted in DSH having high SGPT during treatment. We have 40 cases of acute leukemia. We divided these patients into two groups one group took ursodeoxycholic acid and vitamins another group took only vitamins for 10 days. All patients who fulfilled the inclusion criteria was screened for eligibility and was enrolled in the study and who do not have any exclusion criteria and parents provide informed consent. At enrollment detailed history was taken, thorough clinical examination performed and findings was recorded in a questionnaire. For all enrolled cases, SGPT, S.bilirubin, PT, complete blood count, USG of HBS was performed. After 10 days of treatment with ursodeoxycholic acid again SGPT level was detected.*
Results: *Among the patients who took ursodeoxycholic acid, SGPT becomes normal in 10 patients, another 5 patients SGPT within 100 to 200 U/L,remaining 5 patients SGPT remains unchanged. In another group who did not took ursodeoxycholic acid, SGPT remains unchanged in all 20 cases.*
Conclusion: *Ursodeoxycholic acid reduces the chemotherapy induced high SGPT level in acute leukemia patient. Future studies with a larger sample size are needed to confirm the efficacy and safety of UDCA in this setting. Hepatic functions should be monitored, and the dose should be adjusted during chemotherapy.*
Keywords*: Acute leukemia, Cross sectional study. Ursodeoxycholic acid (UDCA), Hepatotoxicity, Liver.*

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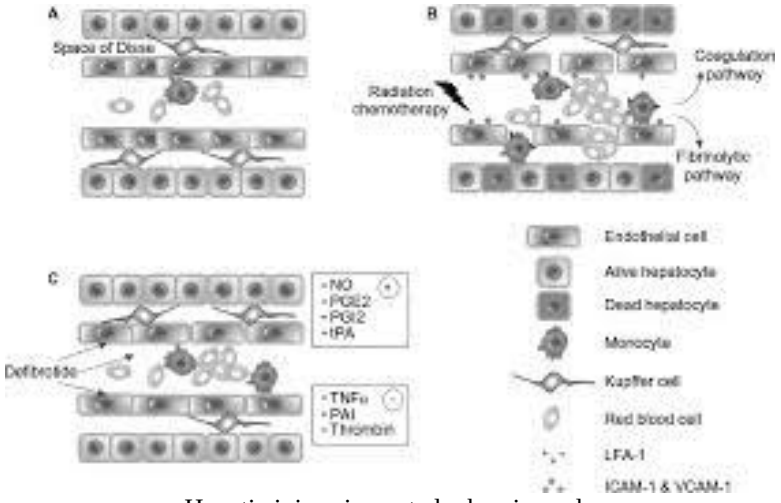
I. Introduction

Liver injury caused by drugs ranges from mild biochemical abnormalities to acute and chronic liver failure. The majority of adverse liver reactions is idiosyncratic, and occurs in most instances 5–90 days after the causative medication was last taken.[1] Almost all anti cancer agents are considered a common cause of drug-induced liver injury.[2] Hepatotoxicity that occurs is usually asymptomatic, transient and associated with hepatic impairment in this period. For acute leukemia at first we use induction chemotherapy for 4 to 6 weeks and hepatic enzymes are more increase during this period. Chemotherapeutic agents causes partial damage in the liver as a result of transient elevation in some biochemical parameters such as AST, ALT, total bilirubin, cholesterol, triglyceride (TG) and Low-density lipoprotein (LDL) as well as transient decrease in albumin and High-density lipoprotein (HDL) concentrations.[3] Ursodeoxycholic acid (UDCA) is one of the secondary bile acids, which are metabolic byproducts of intestinal bacteria and it has anti-oxidative properties.[4] It has extensively been used in clinical practice as a first-line therapy for cholestatic liver diseases.



Hepatic injury in acute leukemia cycle
Source: Google

However, in recent years, a number of clinical and experimental data have shown the beneficial effects of UDCA in noncholestatic liver injury. UDCA prevents damaging the liver mitochondrial functions and preserve its structure in chronic alcohol intoxication.[5] UDCA has been confirmed to improve liver functions in primary biliary cirrhosis (PBC), primary sclerosing cholangitis, pediatric cholestatic disorders, and cystic fibrosis.[6]

II. Objective:

This study aimed to determine the effectiveness of ursodeoxycholic acid for reduction of SGPT in Acute leukemia patients during treatment for continuation of treatment.

III. Materials and methods:

Study site: This was a cross sectional study done in Dhaka Shishu Hospital, Sher-e-Bangla Nagar, Dhaka-1207,over 12 months from July 2013 - June 2014.

Study population: We include the patients with acute leukemia admitted in DSH getting chemotherapy with high SGPT as study group. We excluded the patient with acute leukemia getting irregular treatment. Our sample size was 40. We divided the patients into two groups-one group received vitamin and ursodeoxycholic acid (UDCA) and another group received only vitamin for 10 days.

Study procedure: All acute leukemia patients who fulfilled the inclusion criteria was enrolled in the study and who do not have any exclusion criteria and parents provide informed written consent. At enrollment detailed history was taken, thorough clinical examination performed and findings was recorded in a questionnaire. For all enrolled cases, complete blood count, liver function tests, ultrasonography of HBS and viral screening if needed was done.

Data analysis: The data was analyzed according to standard procedure. SPSS version 12.0 for Windows (SPSS Inc, Chicago, IL, USA) software was used for data entry and analysis. Results of the findings was verified by conducting standard tests for significance (p-value < 0.05), including unpaired student T-test and Chi-square (χ^2) tests, as appropriate.

Ethical issue: After explaining the procedures of the study to the parents/caregivers, informed written consent was taken. Assurance was given to the parents about the drug that have no adverse effect & treatment strategy would not be hampered during this procedure. All financial cost was paid by the researcher. Permission from ethical board of Dhaka Shishu Hospital was taken prior to the work.

IV. Results

Results: Among the patients who took ursodeoxycholic acid, SGPT becomes normal in 10 patients, another 5 patients SGPT within 100 to 200 U/L,remaining 5 patients SGPT remains unchanged. In another group who did not took ursodeoxycholic acid, SGPT remains unchanged in all 20 cases.

Table-1: Age distribution of study population (N=40).

Age	Number	Percentage
2-3 years	17	**42.5%**
3-6 years	10	**25%**
6-9 years	13	**32.5%**
Total	**40**	**100%**

** Among all 40 cases 17(42.5%) were within 2 to 3 years age group, 10(25%) were 3-6 years age and 13(32.5%) were 6-9 years age.

Table-2: Gender distribution of study population (N=40).

Sex	Number	Percentage
Female	12	**30%**
Male	28	**70%**
Total	**40**	**100%**

** Among all 40 patients, 28 (70%) male & 12(30%) female ALL patients, which indicate male predominant. The ratio is M: F-2.3.1

Table-3: Characteristics of study population (N=40).

Patient characteristics		Number of patient	Percentage
Fever during admission	**Present**	40	100%
	Absent	0	0%
Bone pain	**Present**	25	62.5%
	Absent	15	37.5%
Bleeding	**Present**	30	75%
	Absent	10	25%
Lymphadenopahy	**Present**	30	75%
	Absent	10	25%
Splenomegaly	**Present**	35	87.5%
	Absent	5	12.5%
Hepatomegaly	**Present**	36	90%
	Absent	4	10%
Jaundice	**Present**	10	25%
	Absent	30	75%
Vomitting	**Present**	10	25%
	Absent	30	75%

** Among all 40 patients, Fever present in all 40 cases (100%), bone pain present in 25 cases (62.5%), bleeding and lymphadenopathy present in 75% cases, splenomegaly in 87.5%, hepatomegaly in 90% cases, jaundice and vomiting in 25% cases.

Table-4: Hemoglobin (Hb) concentration among study population (N=40).

Hb%	Number	Percentage
< 6 gm/dl	20	**50%**
6-10 gm/dl	15	**37.5%**
>10 gm/dl	05	**12.5%**
Total	**40**	**100%**

** In this study 20(50%) patients Hb was 6 gm/dl (<40%) at the time of diagnosis, Hb was 6-10 gm/dl in 15(37.5%) cases.

Table-5: Total Leucocyte count in study population during admission (N=40).

Total Leucocyte count	Frequency	Percentage
<2500/cumm	2	**5%**
2501-5000/cumm	7	**17.5%**
5001-10000/cumm	7	**17.5%**
10001-20000/cumm	14	**35%**
20001-50000/cumm	6	**15%**
> 50000/cumm	4	**10%**
Total	**40**	**100%**

** Most commonly TC of WBC was 10000-20000/cumm in 14(35%) cases at diagnosis, marked leucopenia (<2500/cumm) was found only in 2(5%) cases.

Table-6: Level of SGPT in study population during treatment (N=40).

Level of SGPT(U/L)	Number of patients	Percentage
100-200	10	25%
200-300	15	37.5%
300-400	8	20%
>400	7	17.5%

** In this study 15(37.5%) patients SGPT was 200-300 U/L, 10(25%) patients SGPT was 100-200 U/L during treatment.

Table-7: Level of S.bilirubin in study population during treatment. (N=40).

Level of S.bilirubin	Number of patients	Percentage
1-2 mmol/L	15	37.5%
2-3 mmol/L	10	25%
3-4 mmol/L	12	30%
>4 mmol/L	3	7.5%

** In this study 15(37.5%) patients S.bilirubin was 1-2 mmol/L, 12(30%) patients S.bilirubin was 3-4 mmol/L during treatment.

Table-8: Virus in the study population during treatment (N=40).

Name of Virus	Number of patients	Percentage
Hepatitis-A	**1**	**2.5 %**
Hepatitis-B	**1**	**2.5 %**
Hepatitis-C	**5**	**12.5%**
No virus	**31**	**77.5%**

** In this study 31(77.5%) patients no virus was isolated.

Table-9: Effect of ursodeoxycholic acid in the study population during treatment (N=40).

Level of SGPT	Patients receiving UDCA	Patients not receiving UDCA
SGPT- decreased	**15(75%)**	**4(20%)**
SGPT-no change	**5(25%)**	**16(80%)**

** This table reveals UDCA significantly reduced SGPT level in acute leukemia patients.

V. Discussion

A total of 40 patients studied among all 40 cases, 17 (42.5%) were within 2 to 3 years age group, 10 (25%) were 3-6 years age & 13(32.5%) were 6-9 years. The duration of fever ranged from 7 days to 150 days. Among them 2(5%) were less than 10 days, 21(52.5%) were 10-50 days & 17(42.5%) were more than 50 days. Bone pain was present in 25 (62.5%) case and absent in 15 (37.5%), which coincide with previous study where it was 65.6%[7]. But in western study it was 25%[8]. Site of bone pain mostly were in multiple site 13 (32.5%) predominantly in lower limbs 9(22.5%) which coincide with previous study. Bleeding manifestation were present in 30(75%) case only. Bleeding sites involved mostly in the gum & skin in about 17(42.5%) it is always secondary to severe thrombocytopenia, caused by marrow failure. Highest risk of bleeding in patient with platelet count <20,000/cumm. Duration of bleeding in most case was less than 5 days (40%). Pallor was present in 100% of case but severity varied. Anaemia was due to marrow failure which was almost due to direct reduction in steam cells and may associated with ineffective erythropoiesis[9].There was no patient found where there was H/O cancer in the family. Lymphadenopathy was present in 23(57.5%) & absent in 17(42.5%) patients. In majority of the patients cervical lymph nodes were involved in 13 (32.5%) others were generalized (27.5%), which coincide with Western study where Lymphadenopathy was in 50% of cases[10].Splenomegaly was found in 35(87.5%) cases & absent in 5(12.5%). It didn't coincide with the previous study where it was 68.8%[8]. Most of the spleen measured within 3-4 cm of the 24(60%) cases and below 2cm in 8(24%).In this study, 20 (50%) patients Hb was 6 gm/dl (40%) at the time of diagnosis,Hb was 40-60% in15(37.5%)cases. In our study among 40 patients only 10 having jaundice and vomiting. Our study not correlated to previous study[11, 12, 13] as they found a rare presentation of leukemia is jaundice. Chemotherapeutic agents causes increase hepatic enzymes. However, an increasing number of evidence indicates that it has risk of elevation of the liver enzyme, cholestatic abnormalities and liver injury as adverse effec[14,15,] and the mechanism of its hepatotoxicity appears to be immunologically mediated.[16] The serum bilirubin, AST, ALT, and ALP are the most sensitive biochemical markers employed in the diagnosis of hepatic dysfunction.[17] In our 40 patients, 25 having SGPT within 100-300 U/L during treatment, but S.bilirubin was increased only in 3 patients. It correlated to previous study by Ishak and Zimmerma[18]. In our 40 patients, virus was isolated only in 7 patients (17.5%) and majority of the cases (5) were hepatitis-c. Our result is not correlated with previous study[19], they found adenoviruses, parainfluenza viruses, rhinoviruses, and enteroviruses and hepatitis c. In our study,UDCA reduced SGPT in 15 patients(75%) among 20 cases which is similar to previous study.[20]UDCA stabilizes the mitochondrial and plasma membranes

of hepatocytes that protect them from various other injuries and it constitute an antiapoptotic action.[21] This protective effect is probably due to its antioxidant action.[22] Previous study showed that UDCA protected mice from liver injury induced by isoniazid plus rifampicin.[23] In addition, UDCA acts an effective hepatoprotective agent against liver dysfunction caused by the broad spectrum antibiotic combination amoxicillin-clavulanic acid[24] and protected rats from liver injury induced by methotrexate, an immunosuppressant drug.[25] In this study we found that chemotherapeutic agents produced a less significant increase bilirubin. The obtained results were not similar to those obtained by others.[20]

VI. Conclusion

The results of the present study demonstrate that UDCA has a hepatoprotective effect against liver injury caused by chemotherapeutic agents owing to their antioxidant and immunomodulatory properties. Further studies with large sample are required to confirm this effect.

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Conflict of interest: The Author has no conflict of interest.

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