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Original Article

Change of lipid profile in children with acute lymphoblastic leukemia due to induction chemotherapy in a tertiary care hospital of Bangladesh

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ABSTRACT

Background: Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy. In the Department of Paediatric Haematology and Oncology of Bangabandhu Sheikh Mujib Medical University (BSMMU), 58% of ALL cases were recorded among 455 newly diagnosed malignancy patients in a single year. Studies found that remarkable hypertriglyceridemia occurs with L-asparaginase therapy and steroid. This study was done to evaluate the changes of serum total cholesterol, triglycerides (TG), high density lipoprotein (HDL), and low-density lipoprotein (LDL) during and after induction chemotherapy in children with ALL.

Methods: This prospective observational study was performed in the Department of Pediatric Hematology and Oncology of BSMMU from March-November 2013. Newly diagnosed acute lymphoblastic leukemia patients aged 3 -15 years were included in this study after having written consent from the parents of the participants to participate in the study and enrolled for the treatment of ALL (according to modified UKALL 2003 protocol).

Results: Total cholesterol, TG, HDL, and LDL changed significantly due to induction therapy. Serum total cholesterol and LDL decreased after completion of L-asparaginse in comparison to before induction, increased significantly after completion of induction in comparison to after completion of L-asparaginase (P=0.001), and increased significantly after induction in relation to before induction therapy (P=0.003). TG decreased significantly (P=0.033) after completion of L-asparaginase than before induction but increased after completion of induction. HDL increased after completion of L-asparaginase and after induction significantly (P=0.001). LDL decreased after completion of L asparaginase which was significant (P=0.005).

Conclusion: After induction chemotherapy, total cholesterol, HDL and LDL level increased and TG level decreased among ALL patients.

Keywords: lipid profile, acute lymphoblastic leukemia

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy around the world.[1] In the United States, the annual incidence of ALL is 1.38 per 100000 population per year. In India, the incidence has been reported as 101.4 per million and 62.3 per million for boys and girls, respectively.[2] Childhood ALL is also common in Bangladesh. In the Department of Paediatric Haematology and Oncology of Bangabandhu Sheikh Mujib Medical University, 58% of ALL cases

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HIGHLIGHTS

1. **L-asparaginase and steroid are the backbone of treatment of acute lymphoblastic leukemia (ALL).**
2. **Induction chemotherapy of ALL in children, lipid profile changes due to L-asparaginase and steroid.**
3. **After induction chemotherapy, total cholesterol, HDL cholesterol and LDL cholesterol level increased, and triglyceride level decreased among ALL patients.**

were recorded among 455 newly diagnosed malignancy patients in a single year.[3]

In the early 1960s, the treatment outcome of leukemia was very poor. Since L-asparaginase has been included in ALL induction treatment, the treatment is continuously improving. Application of therapeutic schedules according to international treatment protocols brought remarkable change of the treatment outcome for children with ALL.[4] The importance of L-asparaginase in the treatment of ALL was demonstrated by Oettgen in 1970.[5]

The Dana Farber Cancer Institute ALL Consortium Protocol 91-01 prolonged asparaginase intensification and the use of dexamethasone improved the outcome of ALL significantly.[6] During the last fifty years, the cure rate for childhood ALL has reached up to 80% and now is exceeding 85%. This advancement is due to treatment strategy with multiagent chemotherapy.[7]

Typically, ALL is treated in four phases- induction therapy, consolidation, maintenance and central nervous system (CNS) directed therapy. There are different protocols for ALL around the globe and the protocol used in the Department of Pediatric Hematology and Oncology of BSMMU comprises– dexamethasone, vincristin, L-asparaginase, daunorubicin, intrathecal methotrexate (MTX), and hydrocortisone with or without cytosine-arabinoside. There are three types of asparaginases used to date which are asparaginase derived from E. coli, pegylated form of the E. coli-asparaginase, and Erwinia asparaginase.[8] L-asparaginase is an effective therapy for specific cases like ALL. The enzyme cuts off the supply of asparagine in the blood and the cancer cells die as they become unable to build their proteins.[9]

Glucocorticoids remain a component of the chemotherapy for a broad spectrum of hematologic malignancies particularly in ALL. Glucocorticoid-induced apoptosis is divided into three stages: an initiation stage which involves glucocorticoid receptor activation and glucocorticoid receptor-mediated gene regulation; a decision stage which engages the prosurvival and proapoptotic factors at the mitochondrial level; and an execution stage which implicates caspases and endonuclease activation.[10] Corticosteroids alter lipid and lipoprotein metabolism by increasing cholesterol synthesis in the liver.[11]

A number of studies found that hypertriglyceridemia occurs remarkably with L-asparaginase theapy.[12] Steinherz in their study found that L asparaginase associated hyperlipidemia is marked, transient and benign.[13] Another study found that L-asparaginase does not raise blood level of triglyceride (TG) and cholesterol.[14] Increased TG levels often are associated with elevated level of increased cholesterol level which subsequently leads to the development of endothelial dysfunction and accelerate the formation of atherosclerotic plaque. Increased hypertriglyceridemia is also associated with an increased risk of pancreatitis.[15] In this perspective, we planned and conducted this study at our department in BSMMU.

The aim of this study was to evaluate the changes of serum total cholesterol, TG, high density lipoprotein (HDL), and low-density lipoprotein (LDL) during and after induction chemotherapy in children with ALL.

METHODS

This longitudinal study was done in the department of Pediatric Hematology and Oncology of BSMMU from March-November 2013. Newly diagnosed ALL patients aged 3-15 years were included in this study after having written consent from their parents according to the policies of the study and were enrolled for the treatment (according to modified UKALL 2003 protocol).

These ALL patients were prospectively evaluated by complete physical examination with serial blood samples including complete blood count, alanine transaminase, serum creatinine, fasting blood sugar, fasting lipid profile (total cholesterol, TG, HDL and

LDL) before starting chemotherapy, and after completion of nine doses of L asparaginase and induction therapy. Children with ALL who had CNS involvement and patients who did not attend the follow up accordingly were excluded from this study. Thirty-five children who fulfilled the inclusion criteria were enrolled in the study. All patients started receiving multi-agent chemotherapy after risk stratification based on white blood cell count, age, and the status of central nervous system.

Two patients were lost in follow up and three children died before completion of L-asparaginase (nine doses) therapy. Finally, data of 30 children were analyzed who completed the induction therapy. Children aged <10 years having total WBC count <50,000/cmm were treated with protocol A, and children aged >10 years having total WBC >50,000/cmm with protocol B.

Our protocol comprised of induction therapy 35 days– oral dexamethasone (days 1-35), vincristin (days 2, 9, 16, 23 and 30), L- asparaginase 6,000 I.U/M2 (days 2-20) every alternate day, daunorubicin- B protocol (days 2,9,16 and 23), 6-mercaptopurin, intrathecal methotrexate (MTX), hydrocortisone and /cytosine-arabinoside (days 28-35). Fifteen patients received oral dexamethasone 10 mg/m2 and 15 patients received 6 mg/m2 (due to modification of protocol). Twenty-two patients were treated according to protocol A and eight patients with protocol B. We used lasparaginase E coli derived (E Medac, made in German). Patients treated with protocol B received daunomycin additionally. Days of interrupted chemotherapy due to infection and other treatment related morbidities during induction therapy was recorded in 17 (56.6%) cases which persisted for 5-15 days.

After all aseptic precaution, 6 ml blood sample was collected from each patient and serum was separated for lipid testing at designated study intervals after fasting 8-12 hours; cholesterol, triglyceride and HDL cholesterol levels were determined by photometric method, and LDL level by calculation with the set programme. PT and APTT were done by photo optical method.

All clinical data including age, sex, height (cm), weight (kg), body surface area (m2), body mass index (BMI), presence of infection, administration of insulin during the induction, family history regarding diabetes, hypertension and treatment history of receiving the antihypertensive, anti-diabetic, and/ lipid lowering agents were recorded in a semi structured questionnaire. Relevant clinical data and laboratory data were collected at diagnosis, after completion of nine doses of L-asparaginase and after completion of induction. Data analysis was done by Statistical Package for Social Sciences (SPSS) software version 15. Statistical significance was set at P< 0.05 and confidence interval was set as 95% level.

RESULTS

Most of the patients, 66.7% were in the age group ≤6 years. Mean age was 6.07 ± 2.95 years and 20 patients (66.7%) were male. Male female ratio was 2:1 **(TABLE 1)**. The range of values of total cholesterol, TG, HDL and LDL before induction, after completion of nine doses L-asparaginase and after completion of induction chemotherapy is shown in **(TABLE 2).** It is depicted from the table that total cholesterol, TG, HDL and LDL were changed significantly due to induction chemotherapy. Serum total cholesterol decreased after completion of nine doses of L-asparaginse in comparison to before induction, increased significantly after completion of induction in comparison to after completion of L-asparaginase (*P*=0.001). TG decreased

TABLE 1 Age and sex distribution of the patients (n=30)

Variables	Frequency	Percent
Age (in year)		
≤6	20	66.7
6-9	6	20.0
>9	4	13.3
Sex		
Male	20	66.7
Female	10	33.3

TABLE 2 Range of cholesterol, TG, HDL and LDL before induction, after completion of nine doses L-asparaginase and after induction

Variable mg/dl	Before induction	After L-asparaginase	After induction
Total cholesterol	73.0-261.0	71.0-284.0	124.0-288.0
Triglyceride	74.0-324.0	53.0-380.0	54.0-291.0
HDL cholesterol	6.0-41.0	5.0-84.0	10.0-93.0
LDL cholesterol	24.0-168.0	31.0-154.0	73.0-168.0

TABLE 3 Comparison of lipid profile before induction of remission, after completion of L-asparaginase and after induction chemotherapy

Variables mg/dl	Before induction	After completion of L-asparaginase	After completion of induction	*P**
Total cholesterol	158.4 ± 42.7	139.5 ± 45.6	195.4 ± 36.6	0.001
Triglycerides	184.5 ± 65.3	136.7 ± 83.4	140.9 ± 62.8	0.019
HDL cholesterol	19.9 ± 10.8	37.2 ± 22.8	50.2 ± 19.6	0.001
LDL cholesterol	101.2 ± 35.0	74.6 ± 32.2	116.7 ± 27.6	0.001

*ANOVA test

significantly (P=0.019) after completion of L-asparaginase than before induction. HDL increased after completion of L-asparaginase and after completion induction significantly (P=0.001). LDL decreased after completion of nine doses of L-asparaginase which was significant (P=0.001) and increased after completion of induction therapy **(TABLE 3)**.

DISCUSSION

Although much improvement in the outcome of ALL has been observed in the last few decades, morbidity and mortality due to adverse effect of component drugs used in induction is a concern. Various adverse effects are observed during the treatment with L-asparaginase like hypersensitivity, dyslipidemia, acute pancreatitis, hyperglycemia, altered liver function and thromboembolic events. Hyperlipidemia may play the key role for the development of thromboembolic manifestation.[10,16] In this study, we evaluated the effect of induction chemotherapy on lipid profile in children with ALL.

ALL evidently peak in incidence at age 2-5 years.[17] The age and sex of our patients were similar to age and sex of the samples of other studies. [18,11,12] In the current study, pretreatment values of total cholesterol, TG and LDL had similarity with the findings of other studies.[19] The evidence of declination of total cholesterol and TG after asparaginase therapy in our series is supported by the observations of Arzinian et al. and Hasan.[16,19]

Hasan found that the mean TG value increases significantly after L asparaginase therapy.[19] We also found TG became lower significantly which is similar to the observation of Arzanian et al. and Oettgen et al.[14,5] In contrast, the results of the study done by Parsons et al. revealed that triglyceride level significantly increased during asparaginase.[12] The increased level of TG could not be explained by consistent above normal value of lipoprotein lipase (LPL) activity and by obesity. Cohen et al. found that the elevated TG levels normalized within two weeks.[11] The mechanism of hypertriglyceridemia is unknown but a relationship with LPL which is inhibited by Lasparaginase might be suggested.[20]

Asparaginase has been reported to cause abnormalities in lipid metabolism ranging from hypocholesterolemia and hypotriglyceridemia to hypercholesterolemia and hypertriglyceridemia during asparaginase therapy. No studies have adequately addressed the mechanism, incidence or severity of these abnormalities.[12] Oettgen in 1970 demonstrated that serum cholesterol decreased after receiving asparaginase required at least one week irrespective of the dose.[5] Elevation of serum total cholesterol levels during treatment has been reported and scientists accredited it to the effect of steroids rather than effect of L-asparaginase. Steroids alter protein and lipoprotein synthesis by increased cholesterol synthesis in the liver.[12] Parsons et al. showed in their study that cholesterol level significantly elevated due to continued steroid treatment. In our study, we also found that after induction of remission, cholesterol level was significantly greater than the initial level reasonably due to continued dexamethasone after completing asparaginase.[12]

It is evident from our results that elevated level of mean cholesterol differed significantly between patients who received dexamethasone 10mg/m^2 and 6mg/m^2. So, it can be assumed that cholesterol change was due to glucocorticoids. We found significant rise of mean HDL level after administering L-asparaginase which

subsequently increased after completion of induction. In contrast, Parsons et al. found HDL levels changed very little with the initiation of asparaginase.[12]

We observed that serum LDL value increased after induction therapy, similar to the results observed by Hasan et al.[18] This may be due to deficiency or defective LDL receptors. So, they remove plasma LDL at much lower rate. We did not get any patient with family history of hyperlipidemia which was similar to finding of Hasan.[19]

According to the observations of Rytting, the incidence of thrombus formation increases with the age of the patient use of central lines.[16] Age group of our patients was lower and central venous catheters were not used. So, there was no remarkable case having evidence of thrombus formation.[16] We did not find any patient with neurological deficit, feature or manifestation cerebral infarction and pancreatitis.

Conclusion

In this study, variations of lipid profile were observed after induction chemotherapy. Total cholesterol, TG, LDL decreased after completion of nine doses L-asparaginase therapy but HDL increased. After completion of induction chemotherapy, total , HDL and LDL cholesterol level increased and TG level decreased. These changes were transient in all cases and no treatment was required.

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Author Contributions

a. Conception and design: RS, CYJ
b. Acquisition, analysis, and interpretation of data: RS, MH, AZMRR, SMS, ZAM
c. Manuscript drafting and revising it critically: RS, SMS, CYJ
d. Approval of the final version of the manuscript, and: CYJ
e. Guarantor accuracy and integrity of the work: RS

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Conflict of Interest

The authors have no conflict of interest to declare.

Ethical approval

The study protocol was approved by the institutional review board of BSMMU (memo no. BSMMU/2013/1636).

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