



EFFECT OF L-ASPARAGINASE IN ACUTE LYMPHOBLASTIC LEUKEMIA ON LIPID PROFILE AND PANCREATIC LIPASE

Areeg Osman Alhaj*¹ and Ayman A.M. ALameen¹

¹Department of Chemical Pathology, Faculty of Medical Laboratory Sciences, University of Khartoum-Sudan.

*Corresponding Author: Dr. Areeg Osman Alhaj

Department of Chemical Pathology, Faculty of Medical Laboratory Sciences, University of Khartoum-Sudan.

Article Received on 07/04/2017

Article Revised on 27/04/2017

Article Accepted on 17/05/2017

ABSTRACT

Background: Dyslipidemia and pancreatitis have been associated with many malignant diseases. Patients with Acute lymphoblastic leukemia on asparaginase therapy may develop pancreatitis and lipid abnormalities. This study done to investigate clinical significance of altered lipid profile in patient with ALL on L- asparaginase therapy. **Methodology:** A prospective study involving 80 patients with different age and gender (25% female, 75% male) patient with ALL (88% T. cell, 12% B. cell) patient divided to two group; 40 (50%) child with age range (1-14 years) and 40 (50%) were adult with age (> 14 years). Fasting serum cholesterol (CH), triglyceride(TG), low density lipoprotein(LDL), high density lipoprotein(HDL) and serum pancreatic lipase, were obtained. **Results:** Eighty patient with acute lymphoblastic leukemia were studied an altered in lipid profile was observed during therapy with L-asparaginase especially(CH,TG,LDL,HDL, Lipase) the means(183.7 mg/dl ,159.8mg/dl), adult (87.5mg/dl, 173.7), (85.9mg/dl, 49.3mg/dl), (24.5mg/dl, 23.8), (43.2 U/L ,49.2 U/L) respectively .After therapy(CH ,TG,LDL,HDL, Lipase) the means were(131.2mg/dl , 137mg/dl), (147.5 mg/dl ,173.7mg/dl), (75.2 mg/dl ,108.4), (40.13mg/dl, 38.9mg/dl), (89.8 U/L,73.0 U/L). Cholesterol level was higher before the initiation of therapy and decreased after therapy. Triglyceride level increases after chemotherapy and these were statistically significant (p-value = 0.000). **Conclusion:** dyslipidemia and pancreatitis associated with L-asparaginase therapy in acute lymphoblastic leukemia.

KEYWORDS: acute lymphoblastic leukemia, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglyceride, lipase.

INTRODUCTION

Abnormal lipid profile and pancreatitis have been associated with various form of cancer including lymphoblastic leukemia.^[1] Acute lymphoblastic leukemia is a malignant disorder of lymphoid progenitor, in which early lymphoid precursor proliferate and replace normal hematopoietic cells of the marrow.^[2-3] There are two main sub type of ALL as categorized by immune phenotype are; B-cell ALL and T-cell ALL.^[4] Asparaginase is a chemotherapeutic agent used in remission induction protocols for treatment of children with ALL. It is a bacterial enzyme isolated from *Escherichia coli* or bacterium *Erwinia Chrysanthemi* and modified pegy-9lated version, PEG-Asparaginase. L-Asparaginase target malignant lymphoblast by depletion of the external source of asparagine, it hydrolyzes L-asparagine to L-aspartic acid and ammonia resulting in depletion of asparagine.^[5] Furthermore, it inhibits protein synthesis by depleting cellular pool of non-essential amino acid. Normal cell can synthesize asparagine via the enzyme asparagine synthase, which lack in malignant lymphoid cell lack.^[6-7]

Asparaginase can be given intravenously or intramuscularly, which is the most commonly route used in children for lowering the risk of sever allergy.^[1]

The most common adverse event of treatment is Pancreatitis, sever hyperlipidemia, altered in liver function, severe allergic reaction and thrombosis.^[5-8-9-10]

Asparaginase associated pancreatitis defined as acute inflammation of pancreas in patient receiving L-asparaginase, its pathology is un known and can cause live threatening complication. According to national protocols L-asparaginase treatment should be discontinued in case of sever pancreatitis.^[5-11] Diagnosis of pancreatitis is based on a combination of clinical, biochemical (amylase, lipase) and radiological evidence. The risk for pancreatitis increases with hypertriglyceridemia.^[5] For that Dyslipidemia, have been observed in majority of ALL patient treated with L-asparaginase in from of; decrease total cholesterol and hypertriglyceridemia this side effect may be explained by a reduce synthesis of lipolytic enzymes (such as hepatic

triglyceride lipase). An alternatively this can be associated with interference in the synthesis of apoE receptors in liver followed by an accumulation of chylomicron remnant.^[12]

The aim of this study was to analyze the effect of L-asparaginase on lipid profile and pancreatic lipase levels before and after the administration of drug.

MATERIALS AND METHODS

A prospective analytical study was conducted in Khartoum state from December (2016) to April (2017) involving 80 subject with different ages and gender from December 2016 to April (2017). All patients were asked to sign an informed consent prior to participate in the study. The laboratory tests were all performed under controlled conditions. Serum cholesterol (CH),

triglyceride(TG), high density lipoprotein cholesterol(HDL-C), low density lipoprotein cholesterol(LDL-C) and pancreatic lipase. Were measured enzymatically (cobas integra 400 plus). normal levels were defined as a serum concentration mg/dl for lipid profile and U/L for lipase. Patient were divided to subgroup children (< 14) and adult (>14). The data were analyzed using SPSS significance level was defined as (p-value <0.05) before and after treatment.

RESULTS

A total of 80 patients, mean duration for child 43.2 day and for adult was 52.35. Mean age for child 6.3 years (range 1-14) and 32.60 for adult. Table (1) and (2) shows the means of lipid profile and pancreatic lipase concentration in treated patient with L-asparaginase.

Table (1): lipid profile and lipase levels in Children before and after L- asparaginase therapy

	Mean	SD
Lipase before	43.28	11.847
CH before	183.75	18.786
TG before	87.53	31.244
LDL before	85.943	19.8185
HDL before	24.50	6.304
Lipase after	89.875	55.1812
CH after	131.28	19.223
TG after	147.50	31.114
LDL after	75.25	18.702
HDL after	40.13	6.227

Table (2) lipid profile and Lipase levels in adult patient before and after L- asparaginase therapy.

	Mean	STD
Lipase before	49.23	48.321
CH before	159.80	36.158
TG Before	173.70	62.589
LDL before	49.35	14.138
HDL before	23.80	4.357
Lipase after	73.05	58.121
CH after	137.83	49.107
TG after	132.13	88.961
LDL after	108.48	14.49
HDL after	38.90	4.241

The mean of CH and TG concentrations in child and adult before treatment were 183.7 mg/dl, 87.5 mg/dl and 159.80 mg/dl, 173.70 respectively. And after treatment were 131.28 mg/dl, 147.50 mg/dl and 137mg/dl, 132.13

respectively. CH level was found to be statistically significant before L-asparaginase therapy (p-value = 0.000). While lipase and TG levels were found to statistically significant after therapy (Table 3,4).

Table (3): significance correlation before and after therapy in children.

	Sig.
Lipase before	.000
Lipase after	
Cholesterol before	.000
Cholesterol after	
Triglyceride before	.000
Triglyceride after	
LDL before& LDL after	.022
HDL before & HDL after	.000

Table (4): significance correlation before and after therapy in adult.

	Sig
Lipase before Lipase after	.000
Cholesterol before Cholesterol after	.000
Triglyceride before Triglyceride after	.000
LDL before& LDL after	.000
HDL before & HDL after	.000

There is no significant relationship between age, duration and child group before and after treatment. While In adults, there is significant relationship between duration

and triglyceride only before therapy (P-value =0.038) table (5).

Table (5): significance correlation of age and duration before and after therapy in adult patient.

	Age	Duration
Lipase before	0.199	0.142
Lipase after	0.246	0.068
CH before	0.368	0.732
CH after	0.293	0.732
TG before	0.554	0.038
TG after	0.661	0.89
LDL before	0.940	0.825
LDL after	0.958	0.774
HDL before	0.315	0.734
HDL after	0.166	0.626

DISCUSSION

The finding of this study showed the association between L-asparaginase therapy and alteration in lipid profile and pancreatitis. The TG, CH, LDL, HDL and lipase were statistically significant (table 3, table 4) these results go in accordance with the finding of other study by Susan K. Parsons, et al which showed significantly higher triglyceride level at all phases before, during and after treatment. while cholesterol level significantly decrease after therapy.^[13] A recent study done by; Einollahi N1, et al showed that the mean total cholesterol, low density lipoprotein cholesterol and high density lipoprotein cholesterol, in all age groups and in both gender, were significantly lower before chemotherapy than after; whereas, mean triglyceride was higher before therapy than after.^[14] And disagree to study conducted by Janan G. Hasan found that mean of serum cholesterol was significantly higher during therapy with L-asparaginase as compared with level before and after therapy.^[1]

S. Sahu, et al (...) had noticed among 915 patients 19(2%) develop pancreatitis. All cases had raised serum amylase and lipase.^[15]

ACKNOWLEDGMENT

I would like to express my deepest gratitude to Alribat university hospital and chemical pathology department.

CONCLUSION

Based on our finding, lipid profile and pancreatic lipase assessment can be employed as beneficial prognostic

factor in acute leukemia. Furthermore, it can be a simple and fast method for follow up the response to chemotherapy.

REFERENCES

1. Janan G. Haasan. lipid profile in children with acute lymphoblastic leukemia on L. asparaginase therapy. The medical journal of basrah university, 28: 2.
2. Ching -Hon, Leslie L Robison, A Thomas look. The Lancet, March 2008; 371(9617): 22-28.
3. Karen seiter. acute lymphoplastic leukemia (ALL). Medscape. Updated, Mar 22, 2017.
4. Rachel A. Egler, Sanjay P.Ahuja, Yousif Matloub. L -asparaginase in the treatment of patient with acute lymphoblastic leukemia. journal of pharmacology & pharmacotherapeutic, 7(2): 62-71.
5. Raheel Altaf Raja, Kjeld Schmiegelow, Thomas Leth Frandsen. Asparaginase associated pancreatitis in children. British Journal of Hematology, 159: 18-27.
6. Ashley Hinson, Dorothee Newbern, Corinne M. Linardic. Asparaginase – induced hypertriglyceridemia presenting as pseudo hyponatremia during leukemia treatment, 2014(2014), article ID 635740,5 pages.
7. Nobuko Hijiya, Inge M. van der Sluis. Asparaginase-associated toxicity in children with acute lymphoplastic leukemia. Leuk lymphoma, 2016 Apr 2; 57(4): 748-757.
8. Jose Manuel Vagace1 and Guillermo Gervasini2 Chemotherapy Toxicity in Patientswith Acute

- Leukaemia. The Scientist's Perspective and Challenge ISBN 978-953-307-553-2.
9. B. Meyer; w. Hagen; W. Scheithauer; L.Öhler; G. V. Kornek. L- asparaginase associated hyperlipidemia with hyperviscosity syndrome in a patient with T-cell lymphoplasmic lymphoma. Oxford Academic. 01 April 2003.
 10. Piatkowska-Jakubas B1, Krawczyk-Kuliś M, Giebel S, Adamczyk-Cioch M, Czyz A, Lech Marañda E, Paluszewska M, Pałynyczko G, Piszcz J, Hołowiecki J; Polish Adult Leukemia Group. Use of L-asparaginase in acute lymphoblastic leukemia: recommendations of the Polish Adult Leukemia Group *Pol Arch Med Wewn*, 2008 Nov; 118(11): 664-9.
 11. Alvarez, O.A. & Zimmerman, G. Pegaspargase-induced pancreatitis. *Medical and Pediatric Oncology*, 2000; 34: 200–205.
 12. Minoru Tozuka, Kazuyoshi Yamauchi, Hiroya Hidaka, Tetso Nakabayashi, Nobuo Okumura, Tsutomu Katsuyama. Characterization of HypertriglyceridemiInduced by L-asparaginase Therapy a for Acute Lymfnoblastic Leukemia and Malignant Lymphoma. *Annals of clinical and laboratory science*, 27: 5.
 13. Susan K. Parsons, Stephen X. Skapek, Ellis J. Neufeld, Caroline Kuhlman, Mary L. Young, Mia Donnelly, John D. Brunzell, James D. Otvos, Stephen E. Sallan, and Nader Rifai. Asparaginase-Associated Lipid Abnormalities in Children with Acute Lymphoblastic Leukaemia. *Blood*, March 15 1997; 89(6): 1886-1895.
 14. Einollahi N1, Alizadeh Sh2, Dashti N*1, Nabatchian Fa1, Zare Bovani M1, Abbasi S3, Mohamadian M4, Kashani Khatib Z. Serum Lipid Profile Alterations in Acute Leukaemia Before and After Chemotherapy. Submitted, 2013; 01-05-2013, Accepted: 23-08-2013 10.
 15. S. Sahu, S.saika, S. K. pai and S. H. Advani 1998. L-asparaginase ((Leunase) Induced Pancreatitis in Childhood Acute Lymphoblastic Leukaemia. *Paediatric Haematology and Oncology*; 1998; 15: 6.