The Effects of L-Asparaginase on Blood Triglycerides, Glucose, and Albumin Levels and Coagulation State in ALL Patients in Pediatric Ward

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Abstract- Asparaginase is one of the most important agents in the treatment of ALL. However, it has some side effects including dislipidemia, hyperglycemia, coagulopathy and hepatotoxicity. We studied its side effects on our patients. The effects of L-asparaginase were assessed on 25 new ALL patients (case group) and 25 patients with known ALL who had completed their treatment before. Sixty two percent of cases were male and remainder was female. The mean age of patients was 7.2 ± 3.8 years. In our patients, there was a rise in triglycerides (TG) was seen following L- asparaginase administration (P = 0.02). Also, PT prolongation (P = 0.02) and hypoalbominemia (P = 0.002) were detected which could PT prolongation and hypoalbuminemia may be seen with L-asparaginase therapy that can be prevented with transfusion of FFP. Hypertriglyceridemia is often asymptomatic with no need for therapy.

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Key words: L-asparaginase, ALL, hyperlipidemia, hyperglycemia

Introduction

L-asparaginase or colapase is used widely in the treatment of ALL patients (1, 2). It can disturb protein synthesis in tumor cells by depleting blood asparagines .It passes blood brain barrier just minimally. There are, however, some side effects including type1 hypersensitivity reactions such as cutaneous rashes, hypertriglyceridemia, hypoalbuminemia, coagulopathy, hyperglycemia, and thromboembolic events (2-5). It is safe in pregnancy women but not in lactation. In one study, 67% of new cases of ALL who were on L- asparaginase therapy, had hypertriglyceridemia (6). Some reports, also, showed a striking rise of triglycerides after L-asparaginase treatment (7-9). Some other studies found a relationship between L-asparaginase therapy and coagulation abnormalities (10-12). On the other hand, hyperglycemia following L-asparaginase treatment was shown in some other reports (13, 14). Regarding the fact that L-asparaginase is a main agent in induction treatment of ALL patients, and some reports of on which had showed L-asparaginase side effects previously, this study was conducted to clarify the effects of this drug on serum triglycerides, albumin, and glucose and also coagulation state in our cases.

Patients and Methods

This study was conducted on 50 ALL patients including 25 new patients (case group) who were on L-asparaginase therapy and 25 cases who had previously completed their therapy without receiving L-asparaginase during study (control group) in Dr. Sheikh Hospital, in Mashhad from 2004 through 2005. Before treating with L-asparaginase, blood samples were taken for triglyceride, glucose, albumin and coagulation studies (Stage 1). This was repeated twice every two weeks (Stages 2, 3). Patients with the following criteria were excluded from the study.

1. Any other concurrent malignancies.
2. Patients in control group who needed L-asparaginage.
3. Patients who died during study.
4. Non-cooperating patients.

Data was analyzed statistically with SPSS using t-test and χ^2. P Values below 0.05 were considered significant.

Results

Thirty one cases (62%) were male and 19 cases (38%) were female. There were 50 patients. The mean age of

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Table 1. FBS in case and control groups in 3 stages

FBS	Normal		Normal		Test result
	Case	Control	Case	Control	
	No	No	No	No	
Stage 1	20	19	5	6	$\chi^2 = 0.11$ $P = 0.73$
Stage 2	20	18	5	7	$\chi^2 = 0.43$ $P = 0.50$
Stage 3	17	16	8	4	$\chi^2 = 1.7$ $P = 0.18$

patients was 7.2 ± 3.8 years. Mean FBS in case group was 109.7 ± 44.3 in stage 1, 115.7 ± 52.33 in stage 2 and 148.3 ± 16.85 in stage 3.

According to the table 1, there were no significant differences between case and control groups in FBS of any 3 stages. It was detected that serum triglyceride levels in the case group were significantly higher than those of the control group at stage 2 (174.7, SD-8.10 vs. 143.16, SD10.86), Serum triglyceride levels had a statistically significant difference between case and control groups as shown in table 2.

There were significant differences in serum albumin levels between case and control groups at stages 2 and 3 (3.8±0.46 vs. 4.1 ± 0.41 in stage 2, $P = 0.02$; 3.5 ± 0.37 vs. 4.04 ± 0.36 in stage3, $P = 0.00$).

Table 3 shows that serum albumin in all stages had a significant difference statistically in case and control groups. In regard to table 4, there was a significant prolongation of PT in case group as compared with controls.

Table 2. Serum triglyceride levels in case and control groups

FBS	Normal		Normal		Test result
	Case	Control	Case	Control	
	No	No	No	No	
Stage 1	11	17	14	8	$\chi^2 = 2.9$ $P = 0.08$
Stage 2	11	19	14	6	$\chi^2 = 5.3$ $P = 0.02$
Stage 3	15	19	10	6	$\chi^2 = 1.4$ $P = 0.22$

Table 3. Serum albumin in case and control groups

FBS	Normal		Normal		Test result
	Case	Control	Case	Control	
	No	No	No	No	
Stage 1	6	1	19	24	$\chi^2 = 1.4$ $P = 0.04$
Stage 2	6	1	19	24	$\chi^2 = 1.4$ $P = 0.04$
Stage 3	7	1	18	24	$\chi^2 = 5.3$ $P = 0.02$

Table 4. Comparison between PT in case and control groups

PTT	Normal		Normal		Test result
	Case	Control	Case	Control	
	No	No	No	No	
Stage 1	20	9	5	16	$\chi^2 = 9.9$ $P = 0.002$
Stage 2	15	9	10	16	$\chi^2 = 2.8$ $P = 0.08$
Stage 3	14	12	11	13	$\chi^2 = 0.32$ $P = 0.57$

Table 5. Comparison between PTT in case and control groups

PTT	Normal		Normal		Test result
	Case	Control	Case	Control	
	No	No	No	No	
Stage 1	18	13.5	7	12	$\chi^2 = 2.1$ $P = 0.14$
Stage 2	14	19	11	6	$\chi^2 = 2.2$ $P = 0.13$
Stage 3	13	15	14	10	$\chi^2 = 0.32$ $P = 0.56$

According to table 5, there was not any statistically significant difference in PTT between case group and control group.

Discussion

L-asparaginase therapy can be associated with some side effects including hyperglycemia, hyperlipidemia, coagulation abnormalities, hypoalbominemia, allergic reactions and thromboembolic events (2- 5).

In one study, abnormality in PT, PTT and hypofibrinogenemia was detected. Other studies showed a prolonged PT and decreased serum fibrinogen levels (10, 15). Also, hypofibrinogenemia was shown in other reports (11, 12).

Similar to above studies, PT prolongation was seen in our patients. It may be, at least to some extent, due to synergetic effects of glucocorticoides and L-asparaginase administration and subsequent-hepatotoxicity. This coagulopathy usually is asymptomatic which may be a result of administration of FFP. Also, because of normal PTT in our patients; it seems that liver function is mildly impaired.

Hypertriglyceridemia is another complication of L-asparaginase administration in patients who suffered from ALL. In one study which was performed on 68 patients, 67% of them showed hypertriglyceridemia (6).

Other reports, also, revealed a TG rise during L-asparaginase therapy (7-9). Similarly, in our study, we showed a significant TG increment with L-asparaginase treatment. It may be have some reasons. The first of all is a transient decrease in lipoprotein lipase. The second one is the concurrent glucocorticoide therapy which is performed in these patients and this drug and L-asparaginase reinforce such side effect. Finally, it may be related to improper food regimen. Fortunately, in many cases, this abnormality is asymptomatic and also transient. But patients, in whom clinical manifestations develop, should be treated appropriately. Since the raised serum triglyceride was not so severe, our patients did not develop any signs or symptoms clinically.

Our study revealed that there was no significant relationship between L-asparaginase treatment and hyperglycemia. But some other studies showed its significant relationship (13,14). It is suggested that some malignancies such as ALL can affect the glucose homeostasis.

Hypoalbuminemia is another side effect of L-asparaginase treatment. The same result was shown in our study like as another study (15). The reason of hypoalbuminemia can be due to the hepatotoxic effect of L-asparaginase, and improper diet can potentiate it. Our patients with low serum albumin who were symptom free might have a mild deficit. In conclusion, L-asparaginase has some side effects such as hypertriglyc-

eridemia, coagulopathy including prolonged PT and hypoalbuminemia. Fortunately, in most cases, they are asymptomatic. But these silent side effects should be kept in mind and upon any sign or symptom, appropriate treatment, including drug discontinuation, should start promptly.

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