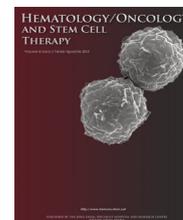




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## LETTER TO EDITOR

# Coagulopathic side effect of L-asparaginase on fibrinogen level in childhood acute lymphoblastic leukemia during induction phase



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### Abstract

**Background:** L-asparaginase is chemotherapeutic agent commonly used in treatment of Acute Lymphoblastic Leukemia. Thromboembolic and to a lesser extent bleeding events are serious complications associated with administration of this drug during the induction phase in ALL especially in children resulting from reduced synthesis of proteins such as Antithrombin & fibrinogen.

**Objective:** Evaluation of the coagulopathic side effect of L-asparaginase during the induction phase in treatment of ALL in children by measuring fibrinogen levels before & after administration of this drug.

**Subjects & method:** An interventional prospective study was performed on 30 newly diagnosed children with ALL, all of them received 9 cycles of L-asparaginase during the induction phase according to UKALL 2003 Protocol.

Fibrinogen was measured before & after treatment with L-asparaginase and the results are compared to a control group of 30 healthy children age & sex matched.

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**Results:** Reduced fibrinogen level is observed in 13 out of 30 patients (43.3%) after treatment with L-asparaginase ranging from 25 to 110 mg/dl with means fibrinogen before & after treatment of  $252 \pm 16.40$  mg/dl &  $158.97 \pm 17.88$  mg/dl respectively ( $p < .0001$ ).

**Conclusion:** Significant reduction in fibrinogen level occurred in childhood ALL patients after treatment with L-asparaginase.

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**Dear editor:** we would like to report our results on the effect of asparaginase on fibrinogen level.

L-asparaginase is a chemotherapeutic agent commonly used in the treatment of both adult & pediatric acute lymphoblastic Leukemia [1]. A major complication of L-asparaginase is alteration in hemostasis resulting in thrombotic events which are well documented in patients receiving this drug [2]. The effect of L-asparaginase on hemostasis during induction phase are less defined in adults than children & most of thrombosis are a symptomatic [3,4].

The coagulation factors & the fibrinolytic factors that are most commonly affected are fibrinogen, factors VII, IX, X, XI and  $\alpha_2$  – antiplasmin [3].

The anticoagulant proteins are also affected at the same time including antithrombin, protein C & protein S & plasminogen raising the incidence of thromboembolic complications over the incidence of bleeding [3].

This study was conducted during the period from May 2016 to October 2016 and included 30 newly diagnosed pediatric patients with ALL. Nineteen of them were males & 11 were females with age range from 2 to 11 years. Thirty age and sex matched controls were recruited from the same hospitals.

Fibrinogen was measured before starting treatment with L-asparaginase and after they had completed treatment with 9 cycles of this chemotherapeutic drug during the induction phase.

Reduced fibrinogen level  $<150$  mg/dL was found in 13 out of 30 patients ranging from 25 to 110 mg/dl (43.3% of ALL patients) after taking L-asparaginase.

The effect of L-asparaginase on fibrinogen is shown in Table 1. Highly significant effect of L-asparaginase on fibrinogen was observed in the patients after taking the drug with a mean fibrinogen level of  $158.97 \pm 17.88$  mg/dL, as compared to mean fibrinogen of the patients before taking the drug which was  $252.00 \pm 16.40$  mg/dL ( $P$  value  $< .0001$ ) & mean fibrinogen of the control group which was  $264.50 \pm 13.95$  ( $P$  value  $< .0001$ ).

Significant reduction in fibrinogen level occurred in 13 out of 30 (43.3%) ALL patients after receiving L-asparaginase. The decrease in plasma level of fibrinogen during the induction phase of ALL treatment is well known coagulopathic side effect induced by L-asparaginase [3,5] & this agrees with results of the studies done by Hunault-Berger et al. [4], Beinart et al. [1], Hongo et al. [5], Tousovska et al. [6], Bettigole et al. [7] & Brodsky et al. [8]. Mathilde Hunault-Berger et al found that in a study of 214 patients treated with L-asparaginase for acute

lymphoblastic leukemia or lymphoblastic lymphoma, antithrombin and fibrinogen levels were lower than 60% and 1 g/L in 71% and 73% of patients, respectively. Twenty thromboses occurred in 9.3% of the patients; Forty-two episodes of bleeding occurred in 31 patients [4].

The mechanism of reduced hepatic synthesis of fibrinogen induced by L-asparaginase is uncertain but probably involves impaired protein synthesis from asparagine depletion [4].

Brodsky et al. gave another explanation for hypofibrinogenemia during L-asparaginase administration which is the production of an intrinsically abnormal fibrinogen with decreased survival after labeling of fibrinogen with [75 Se] Selenomethionine and this explain why bleeding is rare in patients receiving L-asparaginase despite the associated hypofibrinogenemia [8].

Clinically the patients in this study did not show obvious thrombosis or bleeding despite the significant laboratory evidence of hypofibrinogenemia. Absence of bleeding could be due to concurrent impaired synthesis of naturally occurring anticoagulant proteins like protein C & S and plasminogen [4]. Thus the possibility of subclinical thrombosis or bleeding cannot be excluded since most thrombotic events induced by L-asparaginase are asymptomatic [4], especially that those patients were not evaluated by imaging technique e.g. Doppler Venography, Echocardiography or MRI.

The mechanism by which L-asparaginase causes falling in plasma fibrinogen level is reduction of hepatic synthesis of this factor & this proved by the study done by Bettigole RE, et al who used autologous  $^{131}\text{I}$  – fibrinogen in ALL patients receiving L-asparaginase since hypofibrinogenemia could not be ascribed to increased utilization or destruction of fibrinogen [7].

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## Authors' contribution

Professor Alqasim designed the study protocol, interpreted the data, and co-authored the manuscript.

**Table 1** The effect of L-asparaginase on fibrinogen.

Fibrinogen (mg/dl)	ALL patients		Controls
	Before asparaginase	After asparaginase	
Mean	252.00	158.97	264.50
Standard deviation	89.80	97.94	76.40
Standard error of mean	16.40	17.88	13.95
Minimum	150.0	25.0	150.0
Maximum	400.0	400.0	400.0
Mode	150.0	35.0	280.0
Median	225.0	160.0	280.0
P value compared to control	0.546	0.0001*	—
P value compared to before		0.0001*	—

\* Significant using Students-*t*-test for two independent means or paired *t*-test at 0.05 level of significance.

Dr. Al-Khalidi collected cases and controls, carried out tests, and co-authored the manuscript.

All authors approved the final manuscript.

### Conflict of interests

The authors declare no conflict of interests. They received no funds to conduct this study.

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