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ORIGINAL ARTICLE

L-ASPARAGINASE ASSOCIATED TOXICITIES IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA: A SINGLE-CENTER PROSPECTIVE COHORT STUDY

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ABSTRACT

Background: *Acute lymphoblastic leukemia (ALL) is the most common malignancy in children. Asparaginase has played a crucial role in improving the long-term survival. However, the administration of these agents may lead to multifactorial toxicities.So; the objective of this study is to identify the L- asparaginaseassociated toxicity in children with ALL.* ***Methods:*** *This Prospective cohort study was conducted from May 2023 to April 2025 in the Department of Pediatric Hematology and Oncology, Sir Salimullah Medical College Mitford Hospital, Dhaka. A total of 71 children diagnosed with ALL were included in this study.* ***Results*** *Patients aged ≥10 years, WBC count at diagnosis ≥50,000 × 10y /L, receiving Regimen B, body surface area (BSA)>1m² showed increased risk of toxicity in bivariate analysis. In multivariate analysis there was no significantassociation. Hyperglycemia was the commonest adverse reaction followed by hepatic transaminitis and elevated INR. Less frequent reactions included pancreatitis, hyperbilirubinemia, hypersensitivity and hypofibrinogenemia.* ***Conclusion:*** *Hyperglycemia was the commonest toxicities of L-asparaginase in children of more than 10 years, followed by hepatic transaminitis and elevated INR. The less frequent toxicities included pancreatitis, hyperbilirubinemia, hypersensitivity and hypofibrinogenemia.*

Keywords: *L-asparaginase, toxicities, Acute Lymphoblastic Leukemia*

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Introduction:

Acute Lymphoblastic Leukemia accounts for 72% to 75% cases of all childhood leukemia & one fourth of all malignancy in children with a peak prevalence in 2 to 5 years.[1,2] Therehasbeendramaticprogress in the treatment of acute lymphoblastic leukemiadue to combination chemotherapy which containing L-asparaginase. Literally, excellent outcomes have been observed in children withfive-year overall survival (OS) of approximately 90%. This is thought to be due in part to the regimens used in the pediatric population, which generally include agents with more frequent and longer durations of administration. L-asparaginase is included as a main chemotherapeutic agents in several pediatric ALL chemotherapy protocol as a first-line treatment.[3,4]

L-asparaginase is a highly effective chemotherapeutic agents that has become a cornerstone of combination chemotherapy for pediatric patients with ALL. Over the past few years, chemotherapy protocol of young and adolescent children with ALL has been studied closely. Overall survival have been improved due to high-intensity of L-asparaginase.[5,6] L-asparaginase catalyzes the hydrolysis of L-asparagine to aspartic acid and ammo-nia, causing depletion of serum asparagines in the circula-tion. Normal cells are capable to synthesize asparagine and are therefore less susceptible to theaction of L-asparaginase. On the other hand, tumor cells require an external source ofasparagine due to their limited capacity to synthesize it.[7,8]

Currently, three asparaginase preparations are available; two preparations are native, purified from bacterial sources, and one is modified from a native preparation. Thenative preparations are derived from E. coli or Erwiniachrysanthemi. The third preparation, PEG-asparaginase, is also derived from E. coli and is covalently conjugated to monomethoxy- polyethylene glycol, which improves the pharmaco-kinetics of asparaginase. The PEGylated form is better tolerated.[8-10]

Despite the effectiveness of asparaginase as an anti-cancer drug, its use has been associated with several toxicities. L-asparaginase associated toxicity can occurupto 25% of patients. The toxicities of asparaginaseoccurs due to immunologic sensi-tization to the foreign protein, and inhibition of protein synthesis. Common toxicities are allergic reactions, hyperglycemia, pancreatitis, hepatotoxicity, hypertriglyceridemia, diabetes, and coagulopathy. The coagulopathy occurs due to reduced synthesis of fibrinogen, plasminogen, antithrombin III, protein C, and protein S. These can results either bleeding or thrombotic events. Thrombotic events include deep-vein thrombosis, pulmonary embolus and central venous thrombosis.[11-13]

These can cause silent inactivation of L-asparaginasewhich may lead to treatment failure.[14] Several risk factors are associated with L-asparaginase toxicity including age more than 10 years, increased BMI (body mass index), ALL risk categories, hypoalbuminemia, drug accumulation dose. Increase growth hormone secretion and other multifactorial mechanisms are responsible for toxicity in older age group.[5, 15-18]

Results from several studies and clinical trial suggest that L- asparaginase is well tolerated in children and associated with less toxicity. Over the past few years which chemotherapyprotocols of adolescentand young adult age group has been studied comprehensively which containing high dose of L- asparaginase and found that overall survival is better.[19-20]

Several studies showed that children and adolescents less than 10 years of age have been suffered from pancreatitis and thromboembolic complication in comparison to hypersensitivity reaction.[19] Other studies have found that there was no significant relationship of L- asparaginase-associated toxicity with age group.[10-20]However, L- asparaginase-associated toxicity in children with ALL has not been studied separately in Bangladesh.So, the aim of this study is to identify the L- asparaginase-associated toxicity in children with ALL.

Methods:

We performed a prospective cohort study that included 71 patients diagnosed with acute lymphoblastic leukemia at Department of Pediatric Hematology and Oncology in Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh from May 2023 to April 2025.

The inclusion criteria were a diagnosis of ALL according to the WHO criteria[22], age1–12 years, treatment according to the UKALL 2003[21]protocol, and the administrationof at least one dose of L-asparaginase. Children aged less than 1 year or ≥12 years were excluded from this study. All the information regarding the study was collected in a structured questionnaire after taking informed written consent. A total of 75 patients were evaluated for eligibility,but 04 were excluded either because they did not receive at least one dose of L-asparaginase(02 of them due to early death).

Diagnosis of ALL was done on the basis of clinical features, complete blood count with peripheral blood film and bone marrow study. Written informed consent was obtained before enrollment in the study from a parents or guardian.

All patients of ALL were treated with modified UKALL 2003 protocol, regimen 'A' or 'B' according to risk stratification. In addition to this treatment, general supportive care measures were administered to all patients.

The chemotherapy protocol used UKALL 2003[21] provides 9 doses of L-asparaginase at 6000 IU/m^2 on days 04, 06,08,10,12,14,16,18, and 20 during the induction phase. During delayed intensification total four doses of L-asparaginase on days 128, 130, 132 and 134. All the L-asparaginase applications were with a native E. coli-derived preparation, were given intramuscularly.

All patients were monitored regularly from the start of chemotherapy up to 35 days of induction remission for development of toxicity of ALL.

Hypersensitivity skin test was done before giving first dose of L-Asparaginase.Laboratory studies including complete blood count, random blood sugar, activated partial thromboplastin time, prothrombin time, international normalized ratio (INR), alanine aminotransferase, aspartate aminotransferase, creatinine. The amylase and lipase level were tested only if the patients were symptomatic and adverse effects of L-Asparaginasewere suspected.Complete blood count was performed in one day interval. Serum alanine aminotransferase, aspartate aminotransferase and creatinine were performed weekly. Activated partial thromboplastintime, prothrombin time, international normalized ratio (INR) were done after every three doses of L- Asparginase. During this period Fresh frozen Plasma and injection K-one were administered for patients with prolonged partial thromboplastin time, prothrombin time, international normalized ratio (INR).

Data collection included patient demographics, injection-related toxicity and laboratory parameters before administration and up to 35 days of induction of remission or until the resolution of abnor-mal events.

Statistical analyses were performed using IBM SPSS Statistics 26. Data were expressed as frequency, percentage. p-value was reached from Chi-square test. $p<0.05$ is considered level of significant.

Results:

Table I

Patient Demographics and Dosage Information

Characteristic		Patients (N = 71)
Median age, years (range)		8 (2 -13)
	<'10' years	46 (64.8%)
	≥'10' years	25 (35.2%)
Sex	Male, N	59 (83.1%)
	Female, N	12 (16.9%)
Body surface area (mean ± SD)		0.67 + 0.01

A total of 71 patients were included, most of the patients were < 10 years of age (64.8%) and remaining were >10 (35.2%) of age. In this study, 59 (83.1%) patients were male and 12 (16.9%) patients were female. Mean body surface area was 0.67 + 0.01 (Table-I).

Table II

Predictors of L-Asparaginase Toxicity in children with ALL (Bivariate analysis) (n=71)

Factors	Patient with toxicity (n=57)	Patient without toxicity (n=14)	OR	p value
Gender				
Male	48(84.2%)	11(78.6%)	1.46	0.614
Female	9(15.8%)	3(21.4%)	(0.34-6.24)	
Age at diagnosis of ALL (years)				
≥'10' years	24(42.1%)	1(7.1%)	9.45	0.014*
<'10' years		33(57.9%)	13(92.9%)	(1.16-77.3)
WBC at diagnosis of ALL				
WBC ≥50000 × 10^9/L	27(47.4%)	2(14.3%)	0.5.40	0.024*
WBC < 50000 ×10^9/L	30(52.6%)	12(85.7%)	(1.11-26.3)	
Immunophenotype				
B cell	47(82.5%)	12(85.7%)	0.783	0.771
T cell	10(17.5%)	2(14.3%)	(0.151-4.06)	
Regimen used during induction				
Regimen-B	25(43.9%)	1(7.1%)	10.16	0.011*
Regimen-A	32(56.1%)	13(92.9%)	(1.24-82.9)	
CNS disease at diagnosis				
Yes	8(14.0%)	0(0.0%)	-	0.137
No	49(86.0%)	14(100.0%)		
Body surface area				
≥ 1 m^2	21(36.8%)	1(7.1%)	7.58	0.031*
< 1 m^2	36(63.2%)	13(92.9%)	(0.93-62.2)	

Table III

Measurement of risk factors for L-Asparaginase Toxicity in children with ALL (Multivariate analysis)

Factors	p value	OR	95% CI
Age group at diagnosis of ALL (>10 yrs)	.104	6.235	.688-56.472
WBC at diagnosis of ALL (>50000 $\times 10^9$/L)	.091	4.314	.792-23.493
Regimen used during induction (Regimen-B)	.057	8.305	.936-73.679
Body surface area (mean± SD) (>1m^2)	.250	3.761	.394-35.877

Table II showed bivariate analysis of predictors of L-Asparaginase toxicity in children with ALL revealed several significant associations. Gender was not significantly associated with toxicity (OR 1.46, p=0.614). Age at diagnosis showed a significant association, with patients aged ≥10 years having higher odds of toxicity (OR 9.45, p=0.014). WBC count at diagnosis also demonstrated a significant association, with patients having WBC ≥50,000 × 10y /L being at increased risk (OR 5.40, p=0.024). Immunophenotype was not significantly associated with toxicity (OR 0.783, p=0.771). The induction regimen used was a significant predictor, with Regimen-B being associated with higher odds of toxicity (OR 10.16, p=0.011). CNS disease at diagnosis showed no significant association with toxicity (p=0.137). Lastly, body surface area >1m^2 was significantly associated with increased risk of toxicity (OR 7.58, p=0.031).

Table III showed the multivariate analysis of risk factors for L-Asparaginase toxicity in children with ALL revealed no statistically significant independent predictors, although some factors approached significance.

Adverse Reactions in Patients receiving L-Asparaginase

Table IV showed that among patients receiving L-Asparaginase, the most common adverse reaction hyperglycemia (62.0%), followed by hepatic transaminitis (32.4%), and elevated INR (25.4%). Less frequent reactions included pancreatitis (11.3%), hyperbilirubinemia (8.5%), hypersensitivity (4.2%), and hypofibrinogenemia (4.2%).

Mortality Data in Patients receiving L-Asparaginase

Table IV

Adverse Reactions in Patients receiving L-Asparaginase (n=71)

Adverse reaction	Number of patients	Percentage (%)
Hypersensitivity	3	4.2
Hyperglycemia	44	62.0
Pancreatitis	8	11.3
Hyperbilirubinemia	6	8.5
Hypofibrinogenemia	3	4.2
Elevated INR	18	25.4
Hepatic transaminitis	23	32.4

Table V

Mortality Data in Patients receiving L-Asparaginase (n=71)

Outcome	Number of patients	Percentage (%)
Alive	56	78.9
Death	15	21.1
Total	71	100.0

Table V showed among 71 patients receiving L-Asparaginase, 78.9% (56 patients) were alive, while 21.1% (15 patients) death.

Table VI

Association of L-Asparaginase toxicity with mortality (n=71)

Adverse reaction		Outcome			p-value
		Death (n=15)	Alive (n=56)	Total(n=71)	
Hypersensitivity	Present	3(20.0%)	0(0.0%)	3(4.2%)	0.001*
	Absent	12(80.0%)	56(100.0%)	68(95.8%)	
Hyperglycemia	Present	8(53.3%)	36(64.3%)	44(62.0%)	0.438
	Absent	7(46.7%)	20(35.7%)	27(38.0%)	
Pancreatitis	Present	5(33.3%)	3(5.4%)	8(11.3%)	0.002*
	Absent	10(66.7%)	53(94.6%)	63(88.7%)	
Hepatic transaminitis	Present	7(46.7%)	16(28.6%)	23(32.4%)	0.184
	Absent	8(53.3%)	40(71.4%)	48(67.6%)	
Hypofibrinogenemia	Present	0(0.0%)	3(5.4%)	3(4.2%)	0.360
	Absent	15(100.0%)	53(94.6%)	68(95.8%)	
Hypoalbuminemia	Present	1(6.7%)	5(8.9%)	6(8.5%)	0.780
	Absent	14(93.3%)	51(91.1%)	65(91.5%)	
Elevated INR	Present	5(33.3%)	13(23.2%)	18(25.4%)	0.424
	Absent	10(66.7%)	43(76.8%)	53(74.6%)	

p-value obtained by Chi-square, p<0.05 was considered as a level of *significant

Table VI showed the association between L-Asparaginase toxicity and mortality reveals significant relationships for specific adverse reactions. Hypersensitivity was significantly associated with mortality (p=0.001). Pancreatitis also showed a significant association (p=0.002), with 33.3% of deaths in patients who experienced pancreatitis. Other adverse reactions, such as hyperglycemia (p=0.438), hepatic transaminitis (p=0.184), hypofibrinogenemia (p=0.360), hypoalbuminemia (p=0.780), and elevated INR (p=0.424), did not show statistically significant associations with mortality.

Discussion:

Combination chemotherapy containing L-asparaginase has been shown to increase survival rates.

Asparaginase toxicity iscommon in children with ALL may lead to discontinuation of a pivotal component ofa potentially curable disease and eventually decrease survival by15% to 20%. The median age was 8 years. [23-26]

In this study, we evaluated the prevalence and nature of L-asparaginase related toxicities in 71 patients with acute lymphoblasticleukemia (ALL). Additionally, we compared our findings with previousstudies to gain insight into the differences and similarities intoxicity profiles and potential risk factors.

In this study, patients aged ≥10 years having more toxicity in comparison to younger children.In some studies, older age is considered to be associated with an increased risk of asparaginase-related toxicity.[27]A study in Tehran showed that the mean age ofchildren with ALL was 5.5 years and in Brazil, [28] the average age ofchildren at initial diagnosis was 6.3 + 0.5 years. [29] Kakaje*et al.* conducted an epidemiologicalstudy found thata higher proportion of boys with ALL (60.9%) compared to girls developed more hepatotoxicity.

We found that patients having WBC ≥50,000 × 10y / L, using Regimen-B during induction phase of chemotherapy, body surface area ≥1m^2 having increased risk of L-asparaginase-related toxicity in bivariate analysis. In a retrospective cross-sectional study Awwadet al.[10] found that, age, BSA, diagnosis, and PEG-ASP dose were associated with the development of toxicities. Patients diagnosed with high risk ALL and T-ALL displayed a significantly higher likelihood of developing toxicities.[30]

In the multivariate analysis of risk factors for L-Asparaginase toxicity in children with ALL, none of the examined variables reached statistical significance at the conventional threshold (p<0.05). However, several factors demonstrated high odds ratios (OR), suggesting potential clinical relevance.

In this study we found that patients receiving L-Asparaginase, the most common adverse reaction hyperglycemia followed by hepatic transaminitis and elevated INR. Less frequent reactions included pancreatitis, hyperbilirubinemia, hypersensitivity and hypofibrinogenemia. Awwadet al.[10] found that Anaphylaxis/hypersensitivity (36.7%) was the commonest side effects followed by and hepatotoxicity (31.6%), by pancreatitis and hyperglycemia(12.7% each).In a retrospective study Schmidt et al. found the following incidence of asparaginase-associated toxicity: 24.1%clinical hypersensitivity, 19.4% hepatotoxicity, 6.7% hypertriglyceridemia, 4.2% hyperglycemia, 3.7%osteonecrosis, 3% pancreatitis, 2.4% thrombosis, and 1.2% cerebral thrombosis.In this study, we found 21.1% of patients were died.Hypersensitivity and pancreatitis were significantly associated with mortality. A retrospective chart review conducted by Ippoliti et al. found that a total of 17 patients died3 deaths were related to sepsis, 2 occurred during bone marrow transplant, 2 from multi-organ failure, and the cause of the other 10 deaths, which occurred during follow-up, could not be verified.[31]

Conclusion:

The risk factors for L-Asparaginase toxicity in children with ALL revealed no statistically significant independent predictors, although some factors approached significance. Hyperglycemia was the commonest adverse reaction followed by, hepatic transaminitis, and elevated INR. Less frequent reactions included pancreatitis, hyperbilirubinemia, hypersensitivity, and hypofibrinogenemia.

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Conflict of Interest:

No author has any conflict of interest to disclose for this manuscript. The authors themselves are responsible for their ideas and views expressed in this article, which do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Ethical Approval:

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of the Sir Salimullah Medical College. Written informed consent was taken from all the patients before taking part of the study.

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