Original Article

Assessment of Coagulopathy in Children with Acute Lymphoblastic Leukemia Receiving L-asparaginase During Induction Phase of Chemotherapy

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Abstract

Background: *Acute lymphoblastic leukemia (ALL) is among the most common and curable cancers in pediatric populations. A notable complication that can occur during its treatment is coagulopathy, often resulting from the use of chemotherapeutic drugs, especially L-asparaginase (L-aspa). This condition has the potential to negatively influence the overall prognosis of the illness.*

Objective: *To assess the frequency, clinical presentations and risk factors associated with coagulopathy in pediatric patients diagnosed with acute lymphoblastic leukemia during induction phase of chemotherapy with L-Asparaginase.*

Materials and Methods: *This observational study was carried out from October 2017 to November 2018 within the Department of Paediatric Haematology and Oncology at BSMMU. The study included children under 18 years of age who were newly diagnosed with acute lymphoblastic leukemia and had received induction chemotherapy that included L-Asparaginase (L-aspa). These patients were then monitored and assessed for coagulopathy.*

Results: *Among the 80 patients studied, coagulopathy was observed in 38 individuals (47.5%). The analysis did not identify age, sex, initial white blood cell count, platelet count, lineage of acute lymphoblastic leukemia (ALL), treatment regimen or neither central nervous system status as risk factors. Notably, patients with T cell lineage ALL exhibited a higher percentage of coagulopathy (69.2%). Dry bleeding i.e. Petechiae, Purpura, Echymosis were the most common bleeding type. Platelet count was found significantly low with bleeding at diagnosis but initial INR, APTT had no significant relation with bleeding. After 2nd, 4th and 6th L-aspa INR and APTT were to be found significantly high in bleeding but they were not found significant in other stages.*

Conclusion: *In this study coagulopathy was found in significant number of cases. Rate of coagulopathy was higher at diagnosis and remains high up to 6th dose of L-aspa. No risk factor for coagulopathy had been identified as significant. Dry bleeding was more common than life threatening wet bleeding. PT and APTT were to be found as significant predictors for bleeding after 2nd, 4th and 6th dose of L-aspa.*

Key words: *Acute lymphoblastic leukemia, L-asparaginase, Coagulopathy.*

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood accounting for 25% of all childhood cancers.[1] It is also most commonly encountered childhood cancer reported from Bangladesh; 58% cases among 455 newly diagnosed children with malignancy were recorded in 2012 from a center.[2] The use of aggressive polychemotherapy protocols in the last 2 to 3 decades have determined a steady improvement of outcome in children with ALL and ALL now being considered as a curable disease in children.[3]

L-Asparaginase(L-Aspa) has been a standard component of paediatric ALL regimens since the 1980s and is usually combined with a corticosteroid, vincristine and intrathecal chemotherapy in induction & was found to improve event-free survival (EFS).[4] Nevertheless as an important drug, the use of L-asparaginase has also several potential toxicities including the risk of thrombosis.[5] Furthermore, the primary disease itself can activate blood coagulation via procoagulant substances or by impairment of fibrinolytic or anticoagulant pathways.[6] Most of the coagulation disorders occur during the induction phase, as treatment is more intense during this initial phase, and, more

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importantly, the disease is still active at the beginning of therapy.[7]

As survival rate of pediatric cancer has improved notably to almost 80% over the last decades; due to improved diagnostic measures and treatment strategies. So, it becomes utmost important to prevent mortality and morbidity of treatment-associated complications, including coagulopathy.[8] There is a lack of research from our country concerning this critical issue related to the treatment of acute lymphoblastic leukemia. In this context this study was designed to identify the potential impact of chemotherapy; L- Aspa as well as disease process itself on coagulation system in children with newly diagnosed ALL during induction period.

Materials and Methods

This study was a prospective observational investigation carried out in the department of Paediatric Haematology and Oncology at Bangladesh Medical University from October 2017 to November 2018. Primary objective of the study was to detect the frequency, clinical manifestations and identify the risk factors of coagulopathy in children with acute lymphoblastic leukemia receiving L-Asparaginase during induction chemotherapy, where secondary objectives were a) to determine the frequency of coagulopathy in children with acute lymphoblastic leukemia receiving L-Asparaginase during induction chemotherapy. b) to observe the clinical manifestations of coagulopathy in children with acute lymphoblastic leukemia receiving L-Asparaginase during induction chemotherapy. c) to identify the risk factors of coagulopathy in children with acute lymphoblastic leukemia receiving L-Asparaginase during induction chemotherapy.

During the one-year study period, eighty children newly diagnosed with acute lymphoblastic leukemia (ALL), aged between 1 and 17.9 years were enrolled after meeting the established case definition criteria; but a) patients with age less than 1 year or more than 18 Years or b) known case of bleeding disorders like Hemophilia, vWD etc. or c) patient who got anti-coagulant therapy or d) previously treated cases were excluded from this study. Informed consent was obtained from the parents or legal guardians of each child after getting clearance from IRB committee of the University. Data were gathered utilizing a pre-designed data collection sheet (questionnaire). Demographic data regarding age, sex, socio–economic status, family history of malignancy had been collected from guardian or parents. Medical data regarding initial presentation at diagnosis, treatment starting date, complication during treatment, type of treatment protocol were compiled. Clinical information about pallor, temperature, pulse, blood pressure, respiratory rate and other general and systemic clinical parameters had been taken.

Chemotherapy was given to all patients with acute lymphoblastic leukemia according to UKALL-2003 protocol after stratifying risk. Regimen-A was given to standard risk group and regimen-B was specified for high risk group. Induction phase is the first phase of the protocol, which comprises of 35 days. In case of regimen A, the chemotherapeutic agent used in induction phase includes oral dexamethasone (dose:6 mg/m^2, on Day 1-28 then taper over 7 days), vincristine (dose: 1.5mg/m^2, IV on Day 2, 9, 16, 23 and 30), L-asparaginase (dose: 6,000 I.U/m^2, IM on Day 4,6,8,10,12,14,16,18,20) ,6-mercaptopurin (75mg/m^2 on Day 28-35),and IT/ TIT (intrathecal methotrexate, hydrocortisone and/or cytosine-arabinoside). However, in regimen-B another drug daunorubicin (25 mg/m^2 on Day 2, 9, 16 and 23) was given additionally. General supportive management like hydration, allopurinol, phosphate binder, oral care, anal care etc had been administered in all patients.

Patients were on regular follow up. Skin survey, oro-nasal examination, urine, stool, cannula or procedure site examination and other physical examination had been done regularly on each patient to see any bleeding event. Baseline CBC, PT, APTT was done before starting chemotherapy along with other routine initial work up including bone marrow study, chest X-ray, CSF study, S. LDH, S. uric acid, S. inorganic PO_4, S. electrolyte, S. calcium, S. ALT, S. creatinine, blood grouping and Rh typing etc. Afterwards, CBC, PT, APTT were assessed again after 2nd, 4th, 6th and 9th dose of L-aspa and after completion of induction. It was considered as Coagulopathy, if international normalization ratio (INR) is ≥1.3 and/or activated partial thromboplastin time (aPTT) is more than 40 sec. If there was coagulopathy, reports were observed regularly up to become normal. PT and APTT were done by Sysmex CA-50 coagulation analyzer in our department of paediatric Haematology & Oncology of BSMMU.

All data were recorded systematically in preformed data collection form. Statistical analysis was performed by using SPSS for windows version 22.0. p value <0.05 was considered statistically significant.

Results

Total 80 children with ALL were included in this study. Among 80 patients, 52 (65%) were male and 28 (35%) were female patients. Male: Female ratio was 1.9:1. Where 40 (50%) were in the age group of <5 years, 29 (36.3%) were in the age group of 5-10 years and 11 (13.8%) were above 10 years. Mean age was 5.87±3.51 years, median age was 4.85 years and range was between 1.50 to 15.0 years. Majority 67(83.8%) were B lymphoblastic and rest were of 13(16.2%) were T cell lineage. There was no patient with mixed lineage ALL.

Coagulopathy was encountered in 38 (47.5%) patients though out the induction phase of chemotherapy. From the beginning of diagnosis from 80 of included patients coagulopathy was found in 15 (18.8%) patients. 11(14.5%) of 76 patients developed coagulopathy after 2nd dose of L-aspa; 11(14.7%) of 75 patients developed coagulopathy after 4th dose of L-aspa, 9(13.4%) of 67 patients developed coagulopathy after 6th dose of L-aspa, 4(6.5%) of 62 patients developed coagulopathy after 9th dose of L-aspa and 5(8.3%) of 60 patients developed coagulopathy at the end of induction of remission. The observed decrease in the total number of patients from 80 to 60 by the end of the study can be attributed to the deaths of 18 patients during different phases of induction, as well as the discharge of two patients who left against medical advice. It is apparently observed that the percentage of coagulopathy is gradually decreasing over the period of induction therapy.

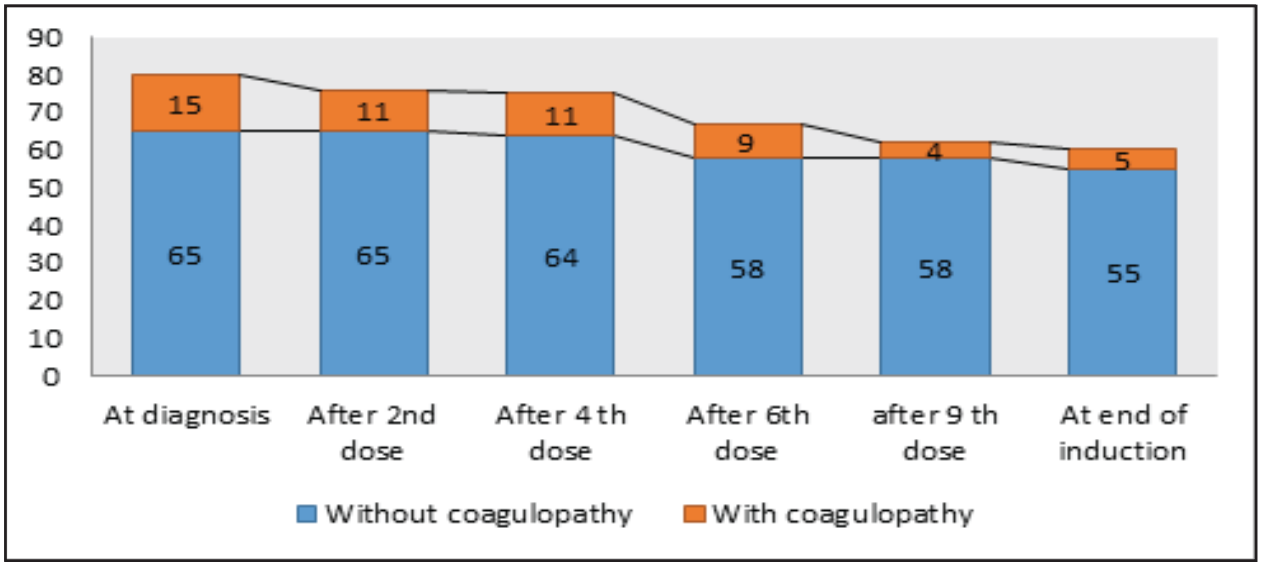

Figure 1: Stacked column chart illustrating the frequency of coagulopathy at various stages of induction chemotherapy in relation to the doses of L-asparaginase.

Following the analysis of the risk associations between various demographic and patient factors and the occurrence of coagulopathy, this study revealed that age, sex, initial WBC count, lineage of acute lymphoblastic leukemia (ALL), treatment regimen, and CNS status could not be classified as risk factors. This conclusion was drawn due to the lack of statistically significant relationships between these factors and the presence of coagulopathy. However the table shows patients with T cell lineage ALL had higher percentage (69.2%) of coagulopathy

Table I: Association of coagulopathy with demographic characteristics (n=80)

Demographic characteristics	n	With coagulopathy No. (%)	Without coagulopathy No. (%)	P value
Age (in years)				
< 5	40	16(40.0%)	24(60.0%)	
5 - 10	29	15(51.7%)	14(48.3%)	0.323 ns
> 10	11	7(63.6%)	4(36.4%)	
Total	80	38(44.6%)	42(55.4%)	
Sex				
Male	52	25(48.1%)	27(51.9%)	0.888 ns
Female	28	13(46.4%)	15(53.6%)	
Initial WBC (per cumm)				
< 50,000	58	26(44.8%)	32(55.2%)	0.437 ns
> 50,000	22	12(54.5%)	10(45.5%)	
Type of ALL				
B cell lineage	67	29(43.3%)	38(56.7%)	0.086 ns
T cell lineage	13	9(69.2%)	4(30.8%)	
Regimen				
Regimen A	46	20(43.5%)	26(56.5%)	0.402 ns
Regimen B	34	18(52.9%)	16(47.1%)	
CNS status				
CNS 1	79	38(48.1%)	41(51.9%)	0.338 ns
CNS 2	1	0(0.0%)	1(100.0%)	

* Data were expressed as frequency and percentage; Chi - square test was done to see the association, ns=not significan

Considering clinical manifestations of coagulopathy bleeding symptoms; At diagnosis, out of 80 patients 37 (46.3%) had bleeding; After 2nd L-aspa out of 76 patients 30 (39.5%) had bleeding, After 4th L-aspa out of 75 patients 27 (36.0%) had bleeding; After 6th L-aspa out of 67 patients 12 (17.9%) had bleeding; After 9th L-aspa, out of 62 patients 1 (1.6%) had bleeding; At end of induction, out of 60 patients 2 (3.3%) had bleeding. The most prevalent forms of bleeding observed in individuals with dry skin types included Petechiae, Purpura, and Echymosis. As well as analysis was conducted on laboratory parameters, including INR, APTT, and platelet counts, in relation to bleeding occurrences during various stages of induction chemotherapy. It was observed that platelet counts were significantly reduced during the initial stage of bleeding; however, initial INR and APTT did not demonstrate a significant correlation with bleeding events. Following the administration of L-asparaginase at the 2nd, 4th, and 6th doses, both INR and APTT levels were significantly elevated in cases of bleeding, although these parameters did not show significant changes in other stages. Additionally, platelet counts did not exhibit a significant relationship with bleeding following L-asparaginase treatment.

Table II: Comparison of INR, APTT and Platelet with and without bleeding in different stages

Stages	n	Bleeding	No bleeding	P value
Initial	80	(n=37)	(n=43)	
INR		1.23±0.66	1.09±0.15	0.208 ns
APTT (sec.)		33.9±12.4	32.1±4.71	0.366 ns
PLT (/cmm)		31016±56126	63523±68440	0.024 s
After 2nd L-aspa	76	(n=30)	(n=46)	
INR		1.52±1.11	1.08±0.11	0.009 s
APTT (sec.)		40.68±20.97	32.83±3.47	0.015 s
PLT (/cmm)		63233±53440	100152±170685	0.255 ns
After 4th L-aspa	75	(n=27)	(n=48)	
INR		1.40±0.76	1.09±0.13	0.007 s
APTT (sec.)		41.8±19.1	32.6±5.54	0.003 s
PLT (/cmm)		57888±53446	72893±60283	0.287 ns
After 6th L-aspa	67	(n=12)	(n=55)	
INR		1.25±0.19	1.13±0.11	0.002 s
APTT (sec.)		39.2±15.9	32.7±2.9	0.006 s
PLT (/cmm)		95166±102671	94545±68128	0.979 ns
After 9th L-aspa	62	(n=1)	(n=61)	
INR		1.27±0.0	1.12±0.11	0.177 ns
APTT (Sec.)		37.0±0.0	32.5±3.63	0.220 ns
PLT (/cmm)		52000.0±0.0	113475±69452	0.383 ns
At end of induction	60	(n=2)	(n=58)	
INR		1.19±0.37	1.08±0.12	0.268 ns
APTT (Sec.)		33.75±8.84	31.35±3.40	0.353 ns
PLT (/cmm)		75500±50204	178275±175319	0.415 ns

***Chi-square test was done to see the association, s= significant, ns=not significant.**

Discussion

Haemostatic disorders observed in children with acute lymphoblastic leukemia are related to changes in vascular function, platelet disorder, liver dysfunction, increased fibrinolysis and DIC. The major haemostatic problem is usually hemorrhaging secondary to thrombocytopenia and procoagulant –anticoagulant imbalance, whereas thrombosis is comparatively less common complication. According to study definition of coagulopathy in this study, out of 80 children with ALL, coagulopathy was encountered in 38 (47.5%) patients and 37(46.3%) had bleeding manifestation; whereas, a previous study on coagulopathy of acute leukemia had shown that 27 patients (40.3%) had bleeding manifestations. 33(49.3%) had some abnormality of global coagulation markers.[9] This finding is consistent with the finding of in this study. According to this study, age, sex, initial WBC count, lineage of ALL, treatment regimen and CNS status could not be considered as risk factor, because those factors had no statistical significant relation with having coagulopathy although patients with T cell lineage ALL had higher percentage (69.2%) of coagulopathy. In larger sample group study; age was found as a significant predictor of coagulopathy, with those aged >30 years at very high risk. T cell lineage ALL and high risk group were also found as risk for coagulopathy.5 A study on experience of AIEOP had shown that male as significant predictor for thrombosis, but age, WBC count, immunophenotype, type of steroid had no significant association.[10]
This current study found that platelet count was significantly low in initial stage bleeding, but platelet count showed no significant relation with bleeding after initiation of treatment; most probably it was due to on-demand platelet transfusion after admission. On the other hand, INR and APTT had significant association with bleeding after 2nd, 4th and 6th L-aspa but they were not found significant in other stages of induction. On other hand in a previous study; mean PT, APTT were higher for leukemia patients with DIC than those without DIC; however, this did not reach statistical significance.[9]

In our study, it is apparently observed that the percentage of coagulopathy as well as bleeding were higher at diagnosis and remain high up to 6th dose of L-aspa then gradually decreasing over the period of induction therapy. The explanation may be the effect of steroid and down regulation of coagulation activation in association with disappearance of peripheral blasts and suppression of inflammatory response.[11] Secondly, gradual decreasing of number of blasts in peripheral blood in earlier stages of induction causes reduced release of procoagulant, which ultimately causes low frequency coagulopathy in later stages. A previous study supported the hypothesis that leukemic blasts activate the coagulation system. They had shown association of peripheral blasts with increased levels of vWF:Ag and parameters of thrombin generation in children with ALL.[12] Third explanation could be due to drop of fibrinogen and antithrombin III levels significantly below baseline values during asparaginase treatment but recover within a week after last administration. So, at the end of induction, percentages of coagulopathy became lower in comparison to earlier stages. The finding is also supported by the conjecture that D-dimer levels were elevated at baseline but improved during induction treatment.[13]

This research was not without its limitations. The limitations of the studies were as follows a) Small sample size of the study population. b)It was a single centre study c)Short duration d) For precise monitoring of coagulation disorder, other investigations like fibrinogen, FDP, D-dimer, antithrombin, factor-V, VII, VIII, IX, X, XI, vWF:Ag etc. needed to be performed, but due to lack of facilities those could not be done in this study. e) Thrombotic events remain undetected. After all, following recommendation could be proposed from this study a) Being cautious for bleeding is needed in first few doses of L-aspa during induction chemotherapy b) Screening tests for coagulopathy like PT and APTT should be done in regular interval during induction to avoid life threatening complication. c) Further study is needed to know about thrombotic manifestations as well as changes in anticoagulant and clotting factors in the population of childhood ALL.

Conclusions

Coagulopathy was found in significant number of cases (47.5%). Rate of coagulopathy as well as hemorrhage was higher at diagnosis and remain high up to 6th dose of L-aspa, then gradually decreasing over the period of induction therapy. No risk factor for coagulopathy has been identified. Dry bleeding was more common than life threatening bleeding. PT and APTT were found as significant predictor for bleeding after 2nd, 4th and 6th dose of L-aspa.

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